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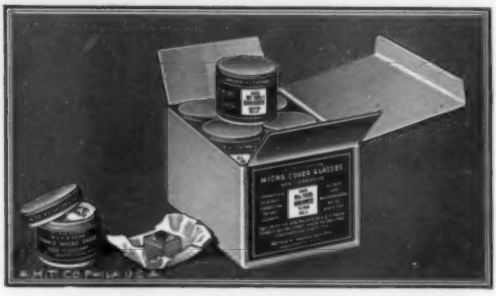

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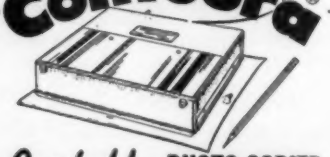

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Engineering Science

IN SEPTEMBER 1952 the engineering societies of this country celebrated a Centennial of Engineering in Chicago. Among the many themes developed, one session sponsored by the American Society of Engineering Education asserted that "The Modern Engineer is a Scientist." Although this may overstate realities somewhat, it does emphasize that there is a well-earned place for engineering among scientific disciplines.

The engineer is becoming increasingly aware that he must depend not only on the tools of the artisan and technician, but indeed upon all the resources of science. The art of engineering continually applies the results of science to the production of goods and services. Furthermore, it constantly demands of science an increasing understanding of natural phenomena to solve its design and development problems.

In order that this interchange between engineering and science may be active and effective, there must be a sense of obligation to engineering by the scientist and a receptive understanding of science by the engineer. Those scientists whose research increases engineering design information comprise the chief contributors to engineering science. They must appreciate and support the engineering objective, but they draw their special knowledge from the field of science.

In considering current technological development the engineering educator is concerned with the role of the engineer as a scientist. Many of the earliest scientists were engineers as well, but with the evolution of engineering education the role of the pure scientist was somewhat removed from practice, even though his services remained essential in the training of the engineer. Today, the rate of application of science is such that the traditional interpretative function of the educator in converting science to engineering is no longer sufficient. There must be someone to provide this service on the job.

It is only to the extent that scientists have become engineers and that engineers have succeeded in being scientists that our recent technical advances have been successful. Although developments in pure science provided the essential foundations for advances in such areas as nuclear energy, supersonic aircraft propulsion, and petroleum chemistry, the progression from laboratory through development to practice could not have occurred in so short a time without this collaboration. With the commercial availability of helium cryostats, still another scientific pressure is demanding active participation by engineers.

The emergency requirements of recent years have drawn many scientists away from basic background studies and have imposed excessive burdens on engineers, but the engineering scientist has shown that the gap between engineering practice and scientific research can be bridged effectively and continuously. In this field the shortage of scientific talent is unusually acute. It can be relieved by increased engineering training at graduate levels and by greater sympathy among scientists for engineering objectives and viewpoints. Engineering scientists in sufficient numbers will not only raise the quality and effectiveness of design and production but also provide many essential services to the increasingly complex facilities for scientific research.

Fortunately there are many among the engineers who fill this role capably. Recent advances in elasticity and plasticity promise radical changes in design practice for structures and machine elements. Chemical and mechanical engineers are continually increasing their fundamental understanding of heat and mass transfer. The field of communications has been remade by the electrical engineers. These achievements embody scientific contributions in that knowledge of physical phenomena is being extended by observation, analysis, and synthesis. The objective, however, remains design information. To the extent that this function is recognized and accepted, progress in both engineering and science will be promoted.

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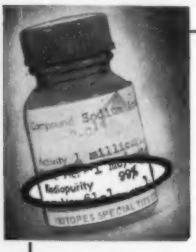

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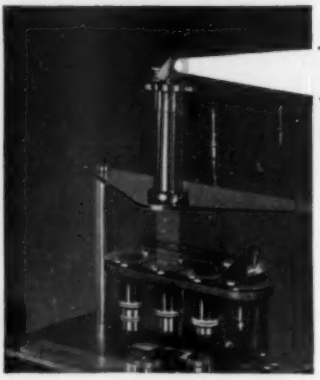

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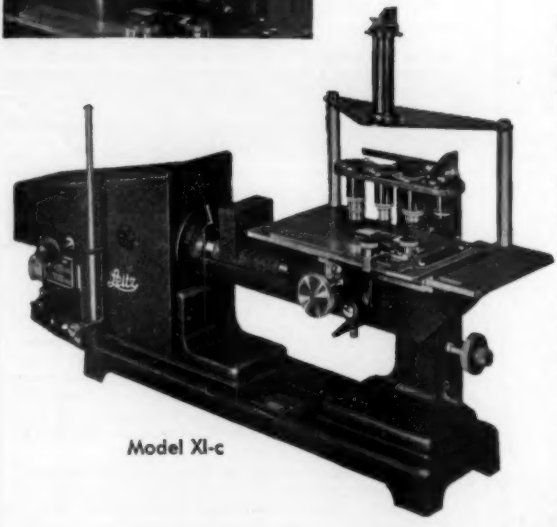

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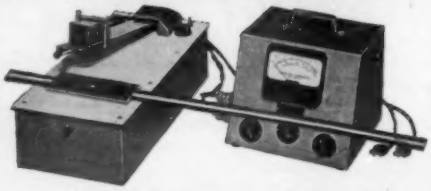

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Radioactive Dust from Nuclear Detonations

Merril Eisenbud and John H. Harley[1]
U. S. Atomic Energy Commission, New York Operations Office, New York

DURING THE PAST TWENTY MONTHS there has been an increase in the tempo of atomic weapons tests. The original facilities of the Atomic Energy Commission's weapons testing program at Eniwetok Atoll have been augmented by the Nevada Proving Grounds, where nuclear detonations occurred in the winter of 1951, fall of 1951, and the spring of 1952.

With each of the programs in Nevada, there have been reports of transient increases in the radioactivity level in many communities of the United States and Canada. These increases are of interest to several groups not connected directly with the Atomic Energy Commission, including scientists engaged in low-level radiation measurements, uranium prospectors, and various segments of the photographic industry. The interest of the latter group began following the world's first atomic explosion in 1945, when Webb (*1*) reported abnormal radioactive contamination of cardboard packaging materials.

In order to assist these groups, as well as to gather scientific information, the Atomic Energy Commission has set up a monitoring program to measure the changes in radioactivity levels caused by nuclear detonations. The purpose of this communication is to describe briefly the monitoring system and to summarize some of the general conclusions that can be drawn from these studies.

Origin of the Increased Radioactivity Levels

The intense heat that accompanies the detonation of a nuclear weapon volatilizes the radioactive fission products as well as the various components of the weapon assembly. This mass of luminescent gas, which forms the "fireball," sucks up varying amounts of dust from the ground by convection. Although some neutron-induced activities may be present in this dust, it is essentially nonradioactive. A portion of the convected material may reach the fireball, and, depending on the existing temperature, some of this dust can be vaporized, or the dust particles can serve as nuclei on which the fireball vapors condense as a radioactive coating. Some of the vapors will condense around ionic nuclei and form discrete fume particles which may or may not aggregate with the larger particles of inactive dust.

[1] The authors wish to acknowledge the extensive assistance rendered by their colleagues in the Atomic Energy Commission. In particular, J. S. Alercio, Hanson Blatz, A. E. Brandt, John C. Bugher, H. J. DiGiovanni, Gordon Dunning, W. B. Harris, W. E. Kelley, P. B. Klevin, H. D. LeVine, D. E. Lynch, and R. S. Morse made important contributions to the design, organization, and execution of the studies. The collection of samples has been greatly facilitated by the cooperation of the U. S. Weather Bureau. The mobile monitoring was made possible by the assignment to our program of personnel and air transport by the Department of Defense.

The total residual radioactivity from the fission products is now contained almost entirely within the head of a mushroom-shaped cloud originating from the fireball. This enormous amount of radioactivity (8.2×10^{11} curies γ-activity 1 minute after detonation of a weapon, equivalent to 20 kilotons of TNT) decays rapidly, and at any subsequent time the activity can be approximated by the relationship $A = A_1 t^{-1.2}$, where A_1 is the activity at one unit of time after the detonation (*2*).

The dispersion of radioactive particulates within the cloud is characterized initially by a wide range of particle size. Particles from less than 1 μ to about 10 μ in diameter are observed to be discrete spheres, whereas the larger particles are more apt to consist of fission products condensed on dust convected from the ground. Included in this portion of the dust are particles of relatively large diameter, often greater than 100 μ.

After the radioactive particles have been carried aloft to great heights (40,000 feet in the case of the Alamogordo explosion) and begin their descent to earth, they are subjected to lateral motion that depends on wind direction and speed. The manner in which a particle descends through various layers of the atmosphere, each characterized by its individual turbulent properties, is not well understood. A 100 μ particle, assuming a density of three, settles by gravity at a terminal velocity of 180 feet/minute; hence sedimentation may play a dominant role in the descent of the relatively large particles. However, a 1 μ particle of the same density will settle at approximately .02 feet/minute—a rate of fall that is not sufficient to explain the rapidity with which such particles reach the ground. It is likely that the turbulent behavior of the atmosphere is a more important factor in the descent of relatively small particles than is gravitational settling. The descent of particles of all sizes is greatly hastened in a region of precipitation where, as with other atmospheric dust, transport to the earth's surface may be accelerated in several ways.

Once they have settled to the surface, the particles may penetrate the earth by infiltration with raindrops. This may be either by simple particle transport or by the slight solubility of the particles.

The elevations in the radiation background observed following atomic detonations are due primarily to the deposition of radioactive dust on the earth's surface. This phenomenon has come to be known as "fallout." At any given location it can be described in terms of the increase in β- or γ-background, or by the quantity of settled radioactive dust (curies or equivalent units) deposited on a given area. In addition, the radiochemical properties of the dust, the concentration sus-

pended in air, and the particle-size distribution of both the suspended and deposited dust are properties that aid in characterizing the phenomenon of fallout and in evaluating its significance.

Description of Monitoring System

The monitoring system from which the data in this report are derived is designed to provide, during scheduled test periods, daily information concerning the presence of abnormal radioactivity in the area of the United States 200 miles and more from the test site. In general, the system comprises a network of 121 monitoring stations located at Weather Bureau stations across the nation and mobile teams equipped to undertake more intensive measurements in the region 200–500 miles from the test site.

Network of fixed monitoring stations. Because of the expense and technical difficulties that would be involved in equipping so large a network with radiation-detection instruments, observations are based on the collection of airborne and settled dust samples, which can be collected with relatively simple equipment and by uniform procedures.

The fixed monitoring stations sample the settled radioactive dust at ground level and, at some locations, the concentration of dust suspended in the air. Sampling is continuous, and once each day the collections are forwarded to the New York Operations Office, where the laboratory of the Health and Safety Division serves as the central counting facility. The dust is allowed to fall onto gummed paper, because this technique gives reasonably reproducible results, and particulates, even when entrained within raindrops, are effectively separated and retained on the gummed surface. At the New York laboratory, the samples are dry-ashed and measured for β-activity. Activities measured at the time of counting are then extrapolated, using the relationship previously given for fission products decay, to the midpoint of the sampling day, and the collection is reported as disintegrations/minute/square foot/24 hours.

The samples of airborne dust are collected on filter papers through which air is passed at a flow-rate of 20 cfm. The processing of the samples in the laboratory is similar to that described above, and the sample is reported as disintegrations/minute/cubic meter of air, representing the average concentration of activity over the 24-hour period.

Mobile monitoring teams. In order to obtain estimates of the maximum fallout in the annular ring 200–500 miles from the test site, mobile monitoring teams are utilized to assure that samples are collected immediately beneath the trajectory of the radioactive debris. The last four bursts in the spring tests in 1952, as well as certain of the tests in the fall of 1951, were monitored in this way.

Guided by meteorological observations made prior to and immediately following a detonation, the mobile teams are deployed at selected ground stations immediately beneath the predicted cloud trajectory. These teams are transported by air and ordinarily arrive at their sampling locations prior to the arrival of the radioactive dust. They sample continuously for a period up to 36 hours following a detonation. By this time the radioactive debris will have cleared the 200–500 mile annulus and, being more widely dispersed, can be adequately sampled by the fixed monitoring stations.

The equipment used by the mobile teams is identical

TABLE 1

List of Weather Bureau Stations Shown in Fig. 1

Code No.	Location	Code No.	Location
0-01	Avalon, Calif.	6-01	Marquette, Mich.
0-02	Los Angeles, Calif.	6-02	Sault Ste Marie, Mich.
0-04	Fresno, Calif.		
0-06	Reno, Nev.	6-03	Escanaba, Mich.
0-08	Elko, Nev.	6-04	Alpena, Mich.
0-09	Salt Lake City, Utah	6-05	Grand Rapids, Mich.
0-10	Flagstaff, Ariz.	6-06	Millbury, Ohio
0-12	Yuma, Ariz.	6-07	Fort Wayne, Ind.
		6-08	Vandalia, Ohio
1-00	Eureka, Calif.	6-09	Louisville, Ky.
1-03	Medford, Ore.	6-10	Nashville, Tenn.
1-08	Boise, Idaho	6-11	Alcoa, Tenn.
1-09	Pocatello, Idaho	6-12	Atlanta, Ga.
1-11	Rock Springs, Wyo.	6-13	Birmingham, Ala.
1-13	Grand Junction, Colo.	6-14	Montgomery, Ala.
		6-15	Mobile, Ala.
1-18	Albuquerque, N. M.		
1-19	Tucson, Ariz.	7-01	Rochester, N. Y.
		7-02	Buffalo, N. Y.
2-01	Ilwaco, Wash.	7-03	Dansville, N. Y.
2-02	Spokane, Wash.	7-04	Dunkirk, N. Y.
2-07	Great Falls, Mont.	7-05	Youngstown, Ohio
2-09	Billings, Mont.	7-06	Charleston, W. Va.
2-12	Rapid City, S. D.	7-07	Lynchburg, Va.
2-13	Scottsbluff, Neb.	7-08	Greenville, S. C.
2-16	Goodland, Kan.	7-09	Florence, S. C.
2-18	Amarillo, Tex.	7-10	Savannah, Ga.
2-19	Roswell, N. M.	7-11	Jacksonville, Fla.
		7-12	Tallahassee, Fla.
3-01	Williston, N. D.		
3-02	Bismarck, N. D.		
3-03	Huron, S. D.	8-01	Dexter, N. Y.
3-05	Norfolk, Neb.	8-02	Oswego, N. Y.
3-06	Concordia, Kan.	8-03	Syracuse, N. Y.
3-07	Wichita, Kan.	8-04	Albany, N. Y.
3-08	Wichita Falls, Tex.	8-05	Binghamton, N. Y.
3-09	Abilene, Tex.	8-06	New York, N. Y. (La Guardia Field)
3-10	Del Rio, Tex.		
4-01	Fargo, N. D.	8-07	New York, N. Y. (AEC Office)
4-02	St. Cloud, Minn.		
4-03	Rochester, Minn.	8-08	Harrisburg State Airport, Pa.
4-04	Des Moines, Iowa		
4-05	Columbia, Mo.	8-09	Wilmington, Del.
4-06	Fort Smith, Ark.	8-10	Baltimore, Md.
4-07	Texarkana, Ark.	8-11	Richmond, Va.
4-08	Port Arthur, Tex.	8-12	Washington, D. C.
4-09	Corpus Christi, Tex.		
5-01	Green Bay, Wis.	9-01	Caribou, Me.
5-02	Milwaukee, Wis.	9-02	Eastport, Me.
5-03	Terre Haute, Ind.	9-03	Mt. Washington Observatory, N. H.
5-04	Memphis, Tenn.		
5-05	Jackson, Miss.		
5-06	New Orleans, La.	9-04	Providence, R. I.
5-07	Peoria, Ill.	9-06	Boston, Mass.

FIG. 1. Radioactivity deposited from tests in spring 1952. Large figures: disintegrations/min/sq foot on Jan. 1, 1953; small figures: station code (see Table 1).

with that provided for the fixed monitoring stations, except that cascade impactors for particle size analysis of the airborne dust are available, as are instruments for measurement of radiation background.

Findings During Tests in the Spring of 1952

The test program conducted in Nevada during the spring of 1952 was a series of eight detonations beginning on April 1 and ending June 4. During this period more than 30,000 samples were collected and evaluated as part of the nationwide monitoring program, and the principal observations and conclusions pending the preparation of more detailed analysis are presented herewith.

Cumulative distribution of deposited radioactivity. Fig. 1 presents the cumulative distribution of deposited radioactivity from the eight explosions in disintegrations/minute/square foot. The data were obtained by extrapolating the activities reported for each of the daily collections to the arbitrary date January 1, 1953, and then summing the extrapolated results from each station. These data thus present the total activity deposited on the surface of the ground as of the given date. Equivalent values for earlier dates can be computed by the factors given in Table 2.

In general, the total fallout shows a geographical variation of two orders of magnitude from 10^2 to 10^4. The area of highest deposition extends northward from the Proving Grounds and includes the stations in northern Nevada and Utah, Idaho, and Montana. The fallout in Salt Lake City occurred almost entirely on one day, May 7, when the passage of the radioactive cloud over Salt Lake City and the surrounding area coincided with rainfall in the region. For the 24-hour period beginning 1130 MST on May 7, the fallout at Salt Lake City was measured at 8×10^6 d/m/ft^2.

TABLE 2

Conversion Factors for Fig. 1

Date	Factor
1/1/53	1
11/1/52	1.4
9/1/52	2.4
8/1/52	3.7
7/1/52	7.4

The fixed monitoring network was arranged in rough arcs centered on the Proving Grounds. The station code numbers are prefixed from 0 to 9, according to the distance from the origin. The mean values for these groups of stations are plotted in Fig. 2. These data fit a smooth curve, except that the values for classes 5 and 8 are high. The maximum activity for each group of stations is also given, and in each class these values are two to four times the mean. A more complete interpretation of the findings must await

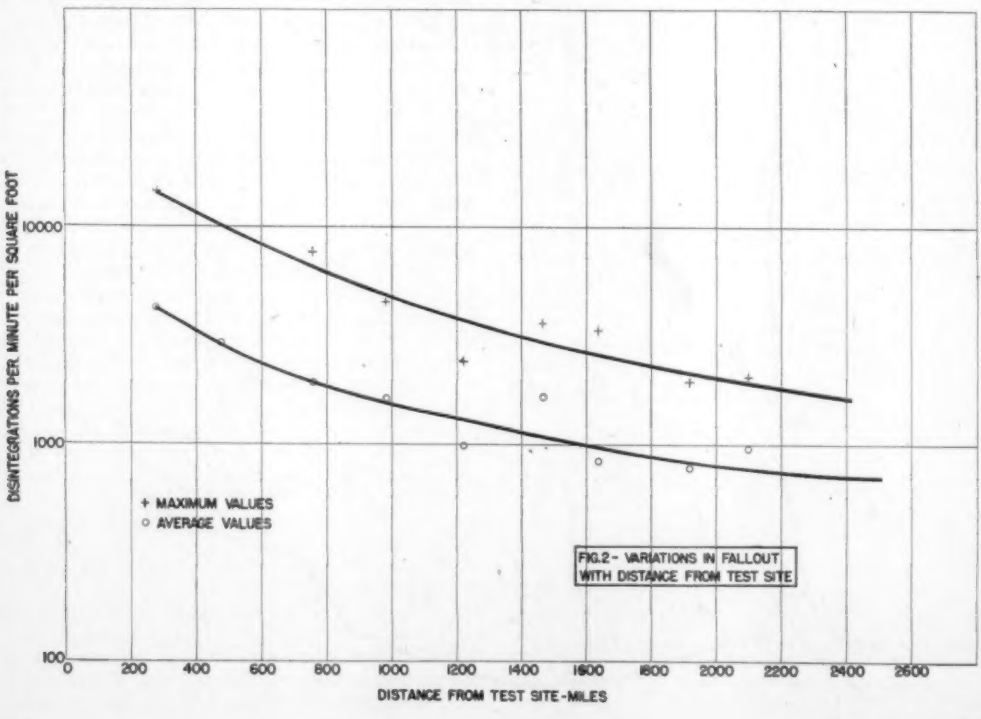


TABLE 3

SUMMARY OF DATA FROM LOCATIONS AT WHICH MAXIMUM FALLOUT WAS OBSERVED BY MOBILE TEAMS

Burst	Airborne dust			Settled dust	
	Locality	Maximum concentration (disintegrations/min/cu meter)	24-Hr av concentration	Locality	24-Hr fallout (disintegration/ft²)
5/ 7/52	Ogden, Utah	510,000	45,000	Wendover, Utah	32×10^6
5/25/52	Price, Utah	27,000	2,200	Grand Junction, Colo.	1×10^6
6/ 1/52	Elko, Nev.	360,000	53,000	Elko, Nev.	4×10^6
6/ 5/52	Elko, Nev.	620,000	30,100	Boise, Idaho	8×10^6

study by the Weather Bureau, where the data are now being analyzed in relationship to meteorological factors.

Measurements by mobile monitoring teams 200–500 miles from proving grounds. Data provided by the fixed stations within the 200–500 mile annulus are augmented by the observations of mobile monitoring teams, which were deployed beneath the trajectory of the radioactive cloud. The initial height of the cloud and the rate of descent of the particles, combined with the lateral motion caused by winds, produce a "skip distance" such that the region of maximum fallout is commonly near the central or outer regions of the annulus. Not only does the fallout diminish at greater distances from the proving ground, but also at closer distances, until one approaches very close to the site of detonation.

Data from the mobile team reporting maximum fallout for each of the four bursts are given in Table 3. The highest concentration of airborne radioactivity does not always occur at the locality having the maximum fallout as measured by settled radioactivity. This is easily understood when it is recognized that the method of collecting dust suspended in air at ground level excludes raindrops that sometimes entrain radioactive particles from higher altitudes. Moreover, a lack of correlation between airborne and settled dust can be attributed to differences in particle size: one extreme limiting case would be a suspension of rapidly falling particles that are too large to be deflected into the air-sampling device or, at the other extreme, a dense suspension of particles too small to be influenced by gravitational settling. The first would appear only as settled dust, whereas the second would appear only as airborne dust. Neither extreme is probable.

Comparison of findings with data from previous weapons tests. The fallout during these tests was slightly higher than the fallout measured during the series in late 1951. The tests held at Eniwetok in early 1951 caused less fallout in the United States than either of the two continental test series for which data are available.

The decay rate of the radioactive dust from each burst of a series follows the exponential time function given previously. During the period of the test program and for a short while thereafter, the decay rates of debris from the successive bursts are markedly different at any given time. As the period of time from the last burst becomes long in relation to the interval between the first and last burst, the decay curves approach a uniform slope and it is possible to consider the accumulation of debris from all bursts as being the same age. Thus, with negligible error, one might arbitrarily select the midpoint of a four-week test program as the time of detonation for all bursts and present in a single decay curve activity vs. time for an indefinite period beginning 60 days from the end of the test series. In Fig. 3 the average fallout in the northeastern United States from each of the three test programs is plotted in this way.

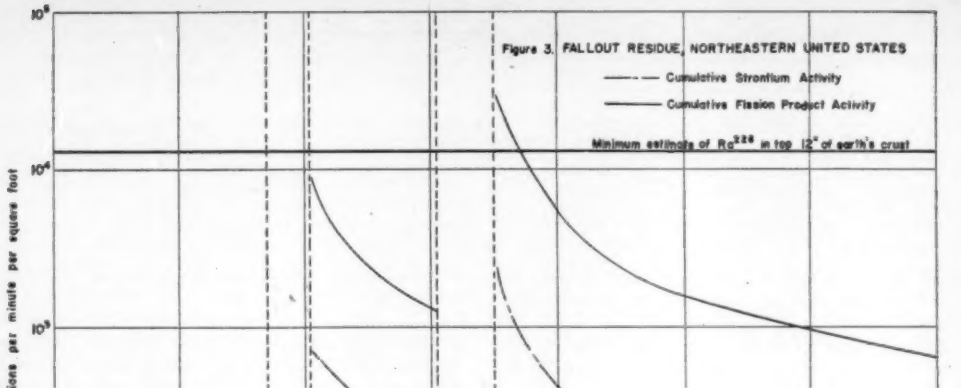
The fallout in this region, from the tests conducted at Eniwetok early in 1951, was of a lower order than that observed for the two Nevada series. Within approximately 200 days this activity had decayed to a level that was no longer significant in comparison with the radioactivity present from the second of the three series. The total activity deposited on unit areas of the earth's surface during the period beyond approximately 200 days, and until the start of the third series, can thus be estimated by the decay curve representing the second test series.

The fallout from the third and most recent series, being of the same order but slightly higher than the second series, is also given. Coexisting on the earth's surface is the fallout from the previous tests, the total being given by the upper decay curve, which thus approximates the activity now present from all three series of tests. The curves are extended until approximately January 1, 1954.

SIGNIFICANCE OF DATA IN RELATION TO THE NATURAL RADIOACTIVE BACKGROUND

A comparison of these data with naturally occurring radioactivity offers a useful means of appreciating the meaning of the data, particularly with regard to their biological significance. Natural radioactivity originates from cosmic sources and from the naturally occurring radioisotopes, of which Ra^{226}, its daughter products, and K^{40} are the most important.

The average concentration of Ra^{226} in soil is of the order of 10^{-13} to 10^{-12} curies/g. Taking the lower concentration as a conservative basis for comparison and limiting our consideration to the top 12 inches of the soil, one calculates that Ra^{226} produces 13,000 d/m/ft² —about 30 times greater than the total residual activ-



ity estimated to be present from the three test series on January 1, 1953. If one includes the entire uranium series, the thorium series, and radiopotassium, a reasonable estimate of the activity naturally occurring in the upper foot of the earth's crust is 10^5 d/m/ft^2.

An estimate of the total activity expressed in this way has little meaning, because it represents the total rate of disintegration of α-, β-, and γ-emitters. Moreover, a comparison of this total with the activity caused by residual fission product radiation is not valid per se, because one must consider the chemical properties of the individual isotopes and the manner in which they enter into biological systems. Of the long-lived fission products, the isotopes Sr^{89-90} are most likely to be absorbed into the body from soil or water, in which fission products are present because of the similarity of strontium to calcium and radium. An estimate of the long-term hazard resulting from the biological uptake of residual fission product activity may therefore be based on a comparison of the strontium component of the fission products with naturally occurring Ra^{226}. The lower decay curve in Fig. 3 plots the activity caused by radiostrontium. This curve is computed from the total fission product decay using data collected by Hunter and Ballou (*3*). The residual radiostrontium is seen to be of a low order compared to the most conservative estimate of the concentration of naturally occurring radium.

Fig. 3 is calculated from the observations of fallout in the northeastern United States, where the mean deposition is approximately 10 per cent of the fallout in areas closer to the Nevada test site. The fission product activities of Fig. 3 should therefore be multiplied by a factor of 10 for an approximation of the residual radioactivity for the regions of maximum fallout.

The fallout measurements are given in disintegration rate units because of the technical difficulties and expense that would be involved in making continuous low-level radiation measurements at a large number of geographically scattered stations. The settled dust measurements do, however, lend themselves to conversion to roentgen equivalent units with the use of data from *The Effects of Atomic Weapons* (*2*). Among the difficulties involved in such a conversion is the fact that the spectral properties of the radiations from mixed fission products are changing constantly with time. For this reason the dose rate from a given activity of fission products is dependent on their age.

Some data are available from measurements made by the mobile monitoring teams. The highest β-γ intensities, measured 3 feet from the ground, were in the range 10–20 mrep/hr, the γ-component being about 10 per cent of the total. These were maximum values associated with fresh deposits of fission products of age 7–15 hours. When the dose delivered by this rapidly decaying activity is integrated from the time of fallout to infinity, the total exposure is ap-

proximately 50 milliroentgens. The γ-dose from *natural* sources is approximately 2 mr/day (*4*). The integrated exposure to the radiation from deposited fission products, under the worst conditions observed, is thus no greater than the dose received from natural radioactivity in a period of 25 days. The present accepted maximum permissible radiation dose rate is 300 mr/week, so the integrated dose from fallout is one sixth that allowed in a week.

As in the case of radioactivity deposited on the earth's surface, the biological significance of radioactive dust suspended in air can likewise be discussed in relation to the radioactivity that is normally present. The airborne dust associated with fallout remains in a given locality for only a few hours, during which its influence on the background radiation level is of a lower order than the rise in background resulting from material deposited on the surface. However, in the case of airborne dust, we must consider the magnitude of the radiation dose to the lung from inhalation of the radioactive particles.

The natural radioactivity of the atmosphere originates almost entirely from radon, which has diffused from the earth. Unpublished measurements in this laboratory indicate that 5×10^{-14} curies/liter of air is a conservative estimate of the radon concentration in normal air. The concentration varies with both geographical and meteorological factors, and is frequently as high as 5×10^{-13} curies/liter. This radioactive gas is present in equilibrium with its daughter products which, because of their initial charge, characteristically adsorb on inert atmospheric dust (*5*). When inhaled, a fraction of this dust is temporarily retained in the lung, and some concentration of the naturally occurring radioactive daughter products of radon is thereby effected. Based on calculations made by Bale (*6*), a radon concentration of 5×10^{-14} curies/liter, in equilibrium with its daughter products, results in a daily lung dose of 10 mrem (assuming a factor of 20 for the relative biological effectiveness of α-particles).

With an approximation of the natural radiation dose to the lung as a basis for comparison, one can now examine the significance of airborne fission products. From Table 3, the highest average concentration of radioactivity observed during a 24-hour period was 53,000 d/m/M³ at Elko, Nevada. The mass median diameter of this dust was approximately 2 μ, which is in the region of optimum particle size for maximum retention in the lung (*7*). The cumulative dose to the lung was calculated (*8*), with assumptions that (*a*) 50 per cent of the dust is retained initially, (*b*) 50 per cent is eliminated from the lung every 90 days, (*c*) the lungs weigh 1000 g, (*d*) the radioactive dust irradiates the lung uniformly, and (*e*) an individual inhales 10 cubic meters of air in the 24-hour period. The approximation of the cumulative dose thus obtained is 20 mrem, equivalent to the dose from the inhalation of normal atmospheric radon daughter products during a two-day period. As was true for whole body irradiation, the dose to the lung from inhaled fission products for maximum fallout is minute when compared to the exposure received in the course of a lifetime from natural sources of radioactivity.

Conclusion

The increases in background radiation sometimes observed at considerable distances from the site of nuclear detonations are due to the deposition of traces of radioactive dust. For brief periods immediately following a detonation, the radioactive background can be markedly increased in some areas, but the cumulative dose from such depositions are minute because of the rapid decay of the activity. The long-lived components of the radioactivity are of a low order compared with the natural radioactivity of the earth's surface and atmosphere.

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News and Notes

Eighth Conference on Iroquois Research

The eighth annual gathering of Iroquoianists, held at Red House, N. Y., Oct. 10–12, again brought together several dozen scholars and scientists from the disciplines that maintain an interest in the anthropology and history of the Iroquoian-speaking Indians of eastern North America. The theme of this year's conference was "Ethnohistory," a choice dictated by the consideration that the Iroquois Indians appear in written accounts from the sixteenth century to the present day. Of necessity, Iroquoian studies have traditionally had a historical consciousness that is impossible for investigations of less adequately documented aboriginal populations. Aware of the widespread interest in a *rapprochement* of history and the social sciences, the program committee (Anthony F. C. Wallace, *chairman*; Martha Randle, John Witthoft, and George Snyderman) felt that discussion of problems and opportunities in Iroquois ethnohistory

would contribute to the development of this cross-disciplinary interest.

This year's program, although basically similar in structure to those of preceding years (see SCIENCE, **114**, 588 [1951] for a more thorough account of the Iroquois conference tradition), featured formally prepared papers and panel discussions. Marius Barbeau, Canadian National Museum at Ottawa, spoke on Indian captivity literature, emphasizing the value of the ethnographic data to be found in this body of early American popular literature. An informal Saturday morning panel, led by John Witthoft, state anthropologist at Pennsylvania Historical and Museum Commission, Harrisburg, provoked discussion of the utility of documentary references in finding "historic" Indian archaeological sites. Although the tediousness of this method, when critically and carefully employed, was recognized as limiting general applicability, it became apparent, nevertheless, from the remarks of several historians and archaeologists present that, without this direct documentation, the sites of several historically known late-contact Indian towns would not have been located at all.

The Saturday afternoon panel presented a set of formal papers on methodological problems of ethnohistory or specific historical events, the adequate investigation of which demanded a blending of historical and ethnological approaches. Wallace (University of Pennsylvania) introduced the session by emphasizing the lesson that anthropologists, sociologists, and psychologists have to learn from historians; that the intensive study of individual events, in which historians are well versed, is a scientific prerequisite to the derivation of general patterns among events, but that a traditional lack of interest in the particular event by social scientists has resulted in the inadequate development both of research techniques and of theory. William N. Fenton (National Research Council) spoke on the problems and promise of a current English translation of Lafitau's *Moeurs des sauvages Ameriquains* (1724) being done under his direction and under the auspices of the American Philosophical Society. Paul A. W. Wallace (Pennsylvania Historical and Museum Commission) presented a careful reanalysis of the vexing problem presented by the Delaware Indians, whom the Iroquois called "women." George Snyderman (anthropologist) discussed general problems of methodology and technique in ethnohistorical work with reference to his survey of historical sources in Philadelphia. Norman Wilkinson (Pennsylvania Historical and Museum Commission) concluded with a careful anaylsis of the circumstances of the notorious Treaty of Big Tree in 1797, when the Senecas sold most of western New York to Robert Morris. On Saturday evening William J. Mayer-Oakes (Carnegie Museum, Pittsburgh) presented an illustrated lecture on the archaeological survey of the upper Ohio Valley which is being undertaken by his museum.

The meetings ended Sunday morning with statements by *rapporteurs* on current field work and digging in the Iroquoian area in the United States and Canada. Iroquois archaeology continues to be active. Iroquois ethnology is now carried on by nearly a dozen anthropologists, working independently, who maintain long-term field work interests on one or another of the reservations.

ANTHONY F. C. WALLACE
Behavioral Research Council
University of Pennsylvania

Scientists in the News

John S. Badeau, president of the American University at Cairo, has resigned, effective with the end of the academic year. **W. Wendell Cleland,** a trustee, will serve as acting president for 1953–54.

Harold S. Black, transmission engineer at Bell Telephone Laboratories, has received the Research Corporation Annual Award for Contribution to Science, in recognition of his invention and development of the negative feedback principle and for contributions to the field of communications.

L. Reed Brantley, head of the Department of Chemistry, Occidental College, will be general chairman of the 123rd national meeting of the American Chemical Society, to be held in Los Angeles Mar. 15–19.

S. Chandrasekhar, University of Chicago astronomer, has been awarded the gold medal of the Royal Astronomical Society of London, for the development of new mathematical tools for the study of astronomy.

Harold E. Cleaves has retired as chief of the Chemical Metallurgy Section, National Bureau of Standards, after 26 years of service in the bureau. He has been chief of the section since 1946.

James Bryant Conant, president of Harvard University, has been selected by President Eisenhower for the post of United States High Commissioner for Germany. Dr. Conant, 23rd president of Harvard, has held that post since 1933, and will become president emeritus Sept. 1.

Harold Eugene Edgerton, professor of electrical engineering, MIT, has received the Franklin L. Burr Prize Award from the National Geographic Society, for his work on stroboscopic lights for use in photography.

Herbert M. Evans, University of California, Berkeley, endocrinologist, has been elected a foreign member of the Swedish Royal Academy of Sciences, in recognition of his researches in endocrinology and vitaminology. Dr. Evans discovered the growth hormone of the pituitary gland and vitamin E.

Herbert S. Fairbank, deputy commissioner of the U. S. Bureau of Public Roads, has been awarded the Roy W. Crum Award for Distinguished Service by the Highway Research Board.

C. M. Ferguson, director of the Ohio Agricultural Extension Service, has succeeded **M. L. Wilson** as director of the Federal Extension Service in the U. S. Department of Agriculture. Mr. Wilson will continue to serve the department as a counselor on extension work in both the U. S. and abroad.

Daniel R. Fisher, of Abingdon, Pa., jet propulsion specialist, and **David S. Blount, Jr.,** of Roanoke, Va., former physicist at the Naval Proving Ground, Va., have been appointed to the Ordnance Engineering Surveillance Team at Duke University.

Hugh W. Gray has been appointed laboratory director of the Du Pont Textile Fibers Department's Pioneering Research Division. Dr. Gray was succeeded by **Allan K. Schneider** as research supervisor in the Chemical Department at the Experimental Station, Wilmington, Del.

Bausch & Lomb Optical Co. has appointed **John D. Hayes** acting head of the Photographic Lens Design Department and named **Erwin Delano** head of the lens design section of the Special Research Department.

Richard A. Howard, who organized and directed the Air Force survival training program in World War II, has been named professor of botany and head of the department at the University of Connecticut. He will succeed **G. Safford Torrey,** who will continue his duties as professor of botany.

John E. Jacobs, manager of the Advanced Development Laboratory, X-Ray Department, General Electric, Milwaukee, has received G-E's Charles A. Coffin Award for 1953. Dr. Jacobs converted cadmium sulfide crystals from a laboratory curiosity into a highly sensitive, automatic detector for inspecting numerous industrial products.

N. A. Khan, government scholar from Pakistan, will join the Chemistry Department, University of Minnesota, as a research fellow under I. M. Kolthoff. Mr. Khan previously completed a project on application of tracer techniques to autoxidation reactions at Ohio State University, and worked on photo-oxidation of fatty materials at the Hormel Institute, University of Minnesota, Austin.

Hazel H. McKay, formerly with the USDA Bureau of Agricultural and Industrial Chemistry, has transferred to the Bureau of Plant Industry, Soils, and Agricultural Engineering, Division of Forest Pathology, Beltsville, Md. She will work with the isolation, culture, and identification of wood-rotting fungi.

Robert James Monroe, associate professor of experimental statistics at North Carolina State College, has accepted appointment as chief of the operations analysis section of the Air Force Missile Test Center, Patrick AFB, Fla.

Raymond J. Nagle has been appointed dean of New York University's College of Dentistry. He was formerly chairman of the Massachusetts State Board of Dental Examiners.

Ernst Oppenheimer, who retired last month as vice president in charge of research after 16 years of association with Ciba Pharmaceutical Products, Inc., will edit future volumes in the collection of medical illustrations published by Ciba for the medical profession. Each atlas in this series contains color reproductions of anatomical and pathological paintings by Frank H. Netter. Dr. Oppenheimer has played an important role in the compilation and publication of past volumes, and the original collection was dedicated to him.

J. Neal Phillips Jr., University of Texas biochemist, has been appointed associate director of research and development for the United States Movidyn Corporation.

Donald D. Ritchie, chairman of the Botany Department, Barnard College, will take an 18-month leave of absence to direct the Naval Research Laboratory Tropical Exposure Station, Canal Zone, Panama. He will study the effects of tropical exposure, weather, and moisture on the growth of fungi, and will direct research in testing paints, fabrics, and insulating materials.

Vincent J. Schaefer, General Electric Research Laboratory weather scientist, has received the 1952 Robert M. Losey award, given annually by the Institute of the Aeronautical Sciences, in recognition of his research in the field of cloud physics and seeding.

Frazar B. Wilde, president of Connecticut General Life Insurance Company, Hartford, has been elected chairman of the Research and Policy Committee of the Committee for Economic Development. He succeeds **Meyer Kestnbaum,** who has been elected chairman of the CED Board of Trustees.

Education

American College of Physicians spring postgraduate courses are scheduled as follows: Feb. 16–21, Pathology and Pathologic Physiology in Internal Medicine, Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation; Mar. 2–7, Studies in the Clinical Aspects and Diagnostic Procedures in Cardiovascular Disease, University of Southern California School of Medicine, Los Angeles; Mar. 9–13, Internal Medicine, Cornell University Medical College and the New York Hospital; Mar. 23–27, Internal Medicine, Mayo Clinic; May 11–15, Controversial Issues in Internal Medicine, the Pennsylvania Hospital, Philadelphia; May 11–16, Electrocardiography, Massachusetts General Hospital, Boston; May 18–22, Internal Medicine, University of Oregon School of Medicine, Portland. All registrations must be made through the college executive offices, 4200 Pine St., Philadelphia 4.

Hebrew Institute of Technology, Haifa, invites

applications for the position of director of the library. Candidates should apply before *Apr. 15* to the national office, 80 Fifth Ave., New York 11.

The Tissue Culture Program of the **Mount Desert Island Biological Laboratory** at Salisbury Cove, Me., consisting of research and training in the aseptic cultivation of plant and animal tissues, embryos, and organs, will be continued from June 15 to Sept. 15. Applications should be sent before *Mar. 15* to Philip R. White, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.

New York University will sponsor its fourth European workshop for American teachers during July and August. Organized on a graduate level, the workshop sessions will include more than two weeks in London, eight days in Heidelberg, four days in Paris, and eight days of travel through Belgium, Germany, Switzerland, and France. As accommodations are limited to 60 people, applications should be sent at once to Christian O. Arndt, School of Education, NYU, Washington Square East, New York 3.

The **U. S. Public Health Service** will offer a short course in phenol determination, Feb. 18–20, and advanced training for sanitary engineers in water pollution abatement programs, Mar. 2–13, at the Environmental Health Center, Cincinnati. Field training courses in rodent control will be given Mar. 23–Apr. 3 and Apr. 20–May 1 at the Communicable Disease Center, Atlanta, and in insect control, Apr. 6–17 and May 4–15.

Wayne University's semiannual Frontiers in Chemistry lecture series will begin Feb. 23 with Allen T. Gwathmey as the speaker. Other speakers will be O. Wintersteiner (Apr. 20), Theald Moeller (Apr. 27), Herbert C. Brown (May 4), Philip J. Elving (May 11), and Harold C. Urey (May 15). The series is cosponsored by the International Society of the Friends of the Kresge-Hooker Library.

Grants and Fellowships

The **American Council of Learned Societies** offers grants for summer graduate study in linguistics at Indiana University and the University of Michigan. Applicants must be U. S. citizens who are graduate students, teachers, staff members of libraries or museums, or government research or policy-making personnel. Application forms, which must be completed by *Apr. 1*, and other information, may be obtained from the council, 1219 Sixteenth St., N.W., Washington 6, D. C.

The **Albert and Mary Lasker Foundation** and the **American Heart Association** have established an annual Albert Lasker Award "for distinguished achievement in the field of cardiovascular diseases." Paul D. White, of Boston, was named as the first winner, and the $1000 prize, a scroll, and a gold statuette of the Winged Victory of Samothrace were presented to him at the 1953 Heart Fund Dinner of the Massachusetts Heart Association in Boston, Feb. 2.

The first three **Louis Lipsky Exchange Fellowships** have been awarded to Charles D. Coryell, of MIT; Gerald Estrin, of the Institute for Advanced Study; and David Ginsburg, of the Weizmann Institute of Science, now on a research fellowship at Harvard. Professor Coryell and Dr. Estrin will go to Rehovoth sometime this year, and Dr. Ginsberg will leave for Oxford later in 1953. The Weizmann Institute established the fellowships in 1951 in celebration of the 75th birthday of Louis Lipsky, American Zionist leader and associate of Dr. Weizmann.

New York University will award research fellowships and assistantships for advanced study in meteorology and oceanography in the College of Engineering. Applicants must have received bachelor's degree by September 1953 and must have had courses in mathematics through differential equations and at least 12 semester hours of physics. Deadline for completed applications is *Apr. 1*.

Oklahoma Medical Research Institute and Hospital is establishing a program of dental research and will offer a fellowship providing a stipend of $4000–$5000 per year. Applicants, who should have one to two years of postdoctorate training, should address Charles D. Kochakian, 825 N.E. 13th St., Oklahoma City.

Meetings and Elections

The **American Academy of Dental Medicine** will hold its annual meeting at the Hotel Shoreham, Washington, D. C., June 26–28. Main theme of the meeting will be "Nutrition."

The **American Association of Hospital Consultants** elected the following officers at its annual meeting in Philadelphia: president, E. M. Bluestone; vice president, Basil C. MacLean; secretary and treasurer, Jacque B. Norman.

Scientific Research Society of America, meeting in St. Louis, elected Wallace R. Brode, Alan T. Waterman, and Edward R. Weidlein members of its Board of Governors for three-year terms beginning July 1. The society's $1000 William Procter Prize for Scientific Achievement was awarded to Shields Warren for his research on the effects of radiation and many other contributions to medical science.

The **Society for Applied Spectroscopy** is seeking papers in any pertinent field for presentation at the annual meeting on May 15. Those who wish to offer papers should get in touch with Van Zandt Williams, Perkin-Elmer Corporation, Norwalk, Conn.

A **Symposium on Molecular Structure and Spectroscopy** will be held at Ohio State University, June 15–19. There will be discussions of the interpretation of molecular spectroscopic data, as well as methods for obtaining such data, and sessions devoted to current developments in spectroscopy. For full information, or a copy of the program, write to Robert A. Oetjen, Department of Physics and Astronomy, OSU, Columbus 10.

Miscellaneous

The **American Geographical Society** has sent an expedition to the Sierra de Perija, on the border between Venezuela and Colombia. William Phelps, Jr., of Caracas, is leader of the expedition, and he is accompanied by Mrs. Phelps and Charles B. Hitchcock, of AGS. The three explorers will search for the headwaters of the Macoita and Aponcito rivers.

Among recipients of the 1952 **Borden Awards** were the following: Emerson W. Bird, American Dairy Science Association; Julius H. Hess, American Academy of Pediatrics; John Wm. Hibbs, American Dairy Science Association; Ralph B. Little, III, American Veterinary Medical Association; E. L. Robert Stokstad, Poultry Science Association; Clara A. Storvick, American Home Economics Association; Carrell H. Whitnah, American Chemical Society. The awards, established in 1936, are administered by professional and scientific associations, and are based on research reported in public documents or scientific journals.

Recent Deaths

Arthur W. Ambrose (63), of Bartlesville, Okla., petroleum geologist, Tulsa, Dec. 28; **Gustave B. Andreen** (72), civil engineer, New York, Dec. 23; **Charles Arden-Close** (87), cartographer, Winchester, Eng., Dec. 19; **Arthur A. Batts** (68), of Niagara Falls, N. Y., industrialist, Clearwater, Fla., Jan. 8; **Gilbert M. Beck** (53), psychiatrist and neurologist, Buffalo, N. Y., Jan. 9; **Truman C. Bigham** (56), of Gainesville, Fla., economist, Dallas, Tex., Dec. 30; **Saul A. Binderman** (60), gastroenterologist, New York, Dec. 30; **Samuel W. Clausen** (64), pediatrician, Rochester, N. Y., Dec. 29; **Samuel Cochran** (81), medical missionary, Newport, R. I., Dec. 26; **Claude C. Coleman** (73), neurosurgeon, Richmond, Va., Jan. 9; **Maria B. Coolidge** (78), physician, Detroit, Dec. 27; **Harold A. Dambly** (53), electrical engineer, Philadelphia, Jan. 15; **Daniel S. Davidson** (53), of Seattle, anthropologist, Altamonte Springs, Fla., Dec. 27; **Antonio Dormea** (—), psychiatrist, Siena, Italy, Dec. 28; **Elaine M. Drew** (66), ornithologist, Barre, Vt., Dec. 22.

Samuel Eglick (61), of Philadelphia, physician, Atlantic City, Jan. 3; **Frederick Fischl** (67), dermatologist, Toledo, Ohio, Jan. 15; **Berthold Flesch** (79), physician, New York, Dec. 28; **William L. Foss** (60), electrical engineer, Washington, D. C., Jan. 11; **Barclay S. Fuhrmann** (67), of Flemington, N. J., physician, Trenton, N. J., Jan. 3; **Edward B. Gallaher** (79), engineer, Norwalk, Conn., Jan. 9; **Fletcher Gardner** (83), physician, San Antonio, Tex., Dec. 22; **Alfred Gordon** (92), neuropsychiatrist, Philadelphia, Jan. 12; **Henry L. Gowens, Jr.** (69), ophthalmologist, Philadelphia, Jan. 2; **G. D. Harris** (—), paleontologist, Ithaca, N. Y., Dec. 4; **John W. Harrison** (36), geologist, Casper, Wyo., Nov. 17; **Paul J. Hatt** (38), of Evanston, Ill., sociologist, Havana, Cuba, Jan. 6; **Earl D. Hay** (66), mechanical engineer, Ames, Iowa, Jan. 1; **Charles H. Herty, Jr.** (56), metallurgist, Bethlehem, Pa., Jan. 17; **William Herbert Hobbs** (88), geologist, Ann Arbor, Mich., Jan. 1; **Grant S. Hopkins** (87), veterinary, Ithaca, N. Y., Dec. 21; **Claude S. Hudson** (71), chemist, Washington, D. C., Dec. 27.

Charles H. Iltis, Jr. (41), neurologist, New York, Dec. 21; **Clara Israeli** (84), pathologist, Philadelphia, Jan. 14; **Thomas A. Jaggar** (81), volcanologist, Honolulu, Jan. 18; **Homer M. Jaquays** (—), mechanical engineer, Montreal, Jan. 9; **Robert Kreys** (36), obstetrician, Pau, France, Jan. 12; **John C. Kurtz** (65), of Bausch & Lomb, Rochester, N. Y., Dec. 27; **W. F. Leech** (77), ear, eye, nose, and throat specialist, Williamson, W. Va., Dec. 27; **Edward A. Looper** (64), eye, nose, and throat specialist, Baltimore, Jan. 14; **Ralph A. Loring** (56), physicist, Louisville, Ky., Dec. 31; **Harold W. Lyall** (64), bacteriologist, Albany, N. Y., Jan. 3; **Francis S. McCaffrey** (64), oral surgeon, New York, Dec. 26; **David W. MacKenzie** (77), urologist, Charlottetown, P. E. I., Dec. 23; **Frank L. McVey** (83), educator, Lexington, Ky., Jan. 4; **Walter L. Maxson** (60), of Duluth, Minn., mining and metallurgical engineer, Bellingham, Wash., Jan. 7; **Charles E. Merriam** (78), political scientist, Rockville, Md., Jan. 8; **Harold Orr** (63), of Edmonton, Alta., dermatologist, Toronto, Dec. 26.

John E. Plunkett (52), of Kingston, Ont., internist, Ottawa, Jan. 11; **Daniel Poll** (65), internist, New York, Dec. 24; **William C. Quinby** (75), urologist, Boston, Dec. 31; **William I. Reardon** (75), internist, Tuckahoe, N. Y., Jan. 15; **Samuel N. Rhoads** (90), of Haddonfield, N. J., ornithologist, Dec. 27; **Thurman B. Rice** (64), public health expert, Indianapolis, Dec. 27; **George W. Rightmire** (84), educator, Columbus, Ohio, Dec. 23; **Ephraim M. Rosset** (39), of Mercon, Pa., obstetrician and gynecologist, Philadelphia, Jan. 1; **Rudolph W. Schroeder** (66), aviation pioneer, Chicago, Dec. 29; **Fred J. Sievers** (72), agronomist, Amherst, Mass., Dec. 26; **Edward H. Skinner** (72), radiologist, Kansas City, Jan. 11; **Arthur R. Smith** (73), electrical engineer, Schenectady, N. Y., Jan. 1; **Albert W. Staub** (72), educator, Santa Barbara, Calif., Jan. 5; **Emerson L. Stone** (57), obstetrician, New Haven, Conn., Jan. 10.

Joseph T. Thwaites (51), of Hamilton, Ont., electronics engineer, enroute from Montreal, Jan. 16; **Edward A. Uehling** (103), mechanical engineer and inventor, West Allis, Wis., Dec. 21; **Harley J. Van Cleave** (66), parasitologist, Urbana, Ill., Jan. 2; **Mark H. Ward** (68), medical missionary, Newton, Mass., Dec. 22; **Jervis B. Webb** (61), industrialist and mechanical engineer, Birmingham, Mich., Dec. 21; **Lewis H. Weed** (66), pathologist and neurologist, Reading, Pa., Dec. 21; **Heston R. West** (92), physician, Phillipsburg, N. J., Jan. 9; **William C. West** (73), mining and highway engineer, New York, Dec. 24; **Francis S. Wilder** (49), economist, Easton, Pa., Dec. 20; **Leland A. Wooten** (52), of Summit, N. J., physical chemist, Williamsburg, Va., Dec. 29.

Technical Papers

Mechanism of Microbial Degradation of Nicotine

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The Central Research Institute,
The Japan Monopoly Corporation,
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As regards the biochemical degradation of nicotine we still lack knowledge, both of the products and of the mechanism of the reaction. Bucherer (*1*) reported the isolation of a purple crystalline substance from a cultural solution containing nicotine, after incubation with three species of *Bacterium*: *B. nicotianum*, *B. nicotinophagum*, and *B. nicotinovorum*; and Wenusch (*2*) found the *N*-methylmyosmine among the degradation products of nicotine. Neither of these two products was, however, satisfactorily characterized. Werle (*3*) studied the decomposition mechanism of nicotine, using livers of guinea pigs, and considered that nicotine probably might be converted first to *N*-methylmyosmine, then to nicotyrin, and further degraded.

We isolated from soil a species of bacteria which probably belongs to *Pseudomonas* and which can utilize nicotine as a carbon as well as a nitrogen source. Using this microorganism we obtained the following results.

The bacterium was cultured at 30° C in a medium containing nicotine (0.2%) (I); KH_2PO_4 (0.1%); $MgSO_4$ (0.05%); $FeSO_4$ (0.3 ml 1% solution/liter); $CaCl_2$ (0.3 ml 1% solution/liter); and $MnSO_4$ (trace). The pH of the solution was adjusted to 6.0, and it was aerated with the aid of an aspirator. After 24 hr incubation the pH value suddenly declined to about 4.6 and the cultural solution abruptly became turbid. Keeping pace with this, the quantity of nicotine diminished rapidly. After this stage the pH value changed little, if at all, and the velocity of consumption of nicotine in the solution diminished.

After 5 days' incubation at 30° C, a 5-liter solution (pH 4.6) was filtered through a celite layer, and the filtrate was evaporated under reduced pressure to about 500 ml. From the ether extract of this condensate we isolated colorless needles (IV) that melted at 161°–162° C. The mother liquor thus treated was then evaporated again to about 100 ml, and from it a purplish-gray powder (VI), which melted at 315° C, was precipitated. The pH of the solution from which substance VI was then filtrated was increased to 8 by the addition of solution of sodium hydroxide. When an ether extract of this solution was evaporated, unchanged nicotine was found. The solution was then made strongly alkaline and again extracted with ether. After the ethereal solution was evaporated, the residual oil was distilled *in vacuo*. The distillate (III), bp 93.5° C (1.5 mm), formed a picrate melting at 127°–130° C after recrystallization from water. When the strong alkaline solution was then acidified and a saturated aqueous solution of picric acid was added to it, a picrate (V) was obtained that decomposed at 316° C.

When dissolved in water, compound IV, which was obtained in colorless needles of mp 161°–162° C, gave a solution of pH 4.4, and when a small quantity was added to a sodium bicarbonate solution the evolution of carbon dioxide was observed, suggesting its acidic nature. The substance gave a strong 2,4-dinitrochlorobenzene reaction, showing a pyridine nucleus, and gave a red coloration with sodium nitroprusside reagent, showing the presence of a carbonyl group. (Anal: Caled for $C_9H_9O_3N$: C, 60.31; H, 5.02; N, 7.82. Found: C, 60.08; H, 5.00; N, 7.44.) It also gave a semicarbazone which decomposed at 202°–203° C. Compound IV gave nicotinic acid (mp 232° C) when oxidized with potassium permanganate.

When substance IV was fused with caustic potash and the resulting mixture was dissolved in water and extracted with ether, the ethereal solution gave almost nothing, even when extracted after acidifying. The acidified solution gave, however, a picrate which melted at over 300° C after recrystallization from 60% methanol. (Anal: Found: C, 27.50; H, 1.44; N, 17.03.) From these properties this compound was identified as the decomposition product V.

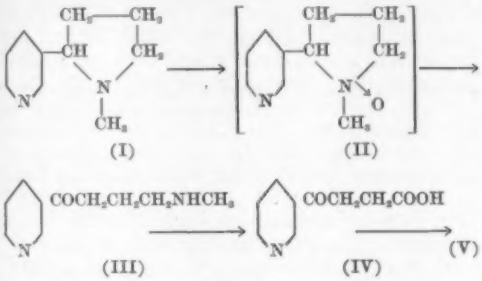
The picrate of III melted at 127°–130° C when recrystallized from water. (Anal: Caled for $C_{22}H_{20}O_{15}N_8$: C, 41.51; H, 3.15; N, 17.61. Found: C, 41.72; H, 3.38; N, 18.51.) When recrystallized from absolute methanol it had a mp of 154°–156° C. The ultraviolet absorption spectrum of III showed maxima at 223 mμ and 263 mμ and minima at 211 mμ and 241 mμ, respectively.

Haines and Eisner (*4*) identified pseudo oxynicotine, first described by Pinner and Wolfenstein (*5*), as 3-pyridyl-3-methyl-aminopropyl ketone. The latter workers prepared this compound by heating oxynicotine (II) with hydrochloric acid in a sealed tube at 140° C. Haines and Eisner further reported on the conversion of pseudo oxynicotine to *N*-methylmyosmine. From their results and also our own, it seems likely that substance III and pseudo oxynicotine are the same, because the characteristics of substance III agree well with those of pseudo oxynicotine. As Haines and Eisner described, the picrate of pseudo oxynicotine melts at 128°–130° C (dipicrate of pseudo oxynicotine) when recrystallized from water and at 158°–160° C (dipicrate of *N*-methylmysomine) when recrystallized from absolute methanol. The ultraviolet absorption spectrum of pseudo oxynicotine showed maxima at 223 mμ and 263 mμ and minima at 211 mμ and 241 mμ, respectively.

Substance IV, which showed the properties of both a weak acid and a ketone, may have the molecular

formula of $C_9H_9O_2N$ and may be derived from pseudo oxynicotine by oxidative activities of the microorganism. This acid seems to be 3-succinoyl pyridine, and its constitution is now being studied by synthesis from nicotinic acid.

From the above-mentioned results we may now assume the mechanism of the decomposition of nicotine by the microorganism as follows:



Substance VI has almost the same characteristics as the compound obtained by Bucherer. (Anal: Found: C, 55.40; H, 4.65; N, 7.68.) Substance V, which may be produced through further decomposition from IV, is not extracted with ether from the acidic or alkaline solution, but from the acidified solution substance V is precipitated as picrate, mp 316° C, when recrystallized from 60% methanol (Anal: Found: C, 27.29; H, 1.34; N, 16.77.)

References

1. Bucherer, H. *Zentr. Bakteriol. Parasitenk., Abt. II*, **105**, 166, 445 (1942).
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4. Haines, P. G., and Eisner, A. *J. Am. Chem. Soc.*, **72**, 1719 (1950).
5. Pinner, A., and Wolfenstein, R. *Ber. deut. chem. Ges.*, **25**, 1428 (1892).

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Influence of Age of Serum on Microbiological Response[1]

E. Staten Wynne and Donald A. Mehl

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During investigations in this laboratory involving microbiological assays of blood from patients with malignant neoplastic diseases, it has been observed that storage of serum significantly influences the degree of response obtained with certain lactic acid organisms.

The basal medium contained 2% glucose and salts as employed by Dunn *et al.* (*1*), but 0.03%–0.05% Difco yeast extract was added in place of the growth factors and amino acids used by these workers. In the absence of yeast extract, significant growth response to serum did not occur. With a yeast extract concentration of 0.03%–0.05%, satisfactory responses to serum were obtained, with minimal growth in the control medium without serum. The nature of the component(s) of serum responsible for the observed stimulation of growth of microorganisms is unknown and, in fact, was not a primary concern of the studies reported here.

Double-strength medium was brought to boiling, filtered, and autoclaved for 15–20 min at 15 psi. Cultures were carried on Difco micro inoculum agar and were usually transferred twice in micro inoculum broth before use. Cells were washed once with distilled water, and 1–2 drops of a 1:100 dilution were used as inoculum. Incubation was at 37° C. Sera were obtained from prisoners at the state penitentiary in Huntsville, Texas, and from employees and patients in this hospital. All sera were presumably fasting. Hemolyzed sera were discarded, since it was noted that such sera yielded abnormally high responses. Growth was estimated, generally from triplicate tubes, in terms of optical density (log L_o/L) calculated from Coleman spectrophotometer readings at 590 μ. Serum concentrations employed ranged up to 25%.

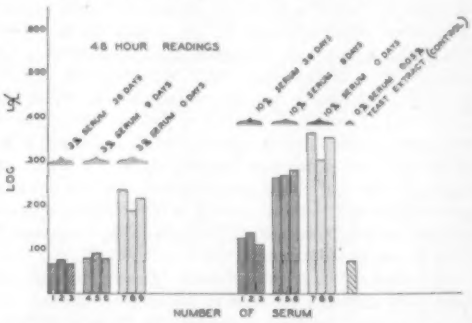

FIG. 1. Variation in response of *L. casei* Texas with age of normal sera.

Three groups of 3 sera each stored at 4° C for 0, 9, and 36 days, respectively, were tested simultaneously at two concentrations with *Lactobacillus casei* Texas (Fig. 1). Two control experiments, one with 10 fresh normal sera and the other with 5 fresh normal sera and 5 fresh sera from cancer patients, failed to show variations approaching the magnitude of those shown in Fig. 1. Responses to sera from patients with malignant neoplastic disease were similar to those obtained with normal sera.

Six pools of sera collected from five volunteers at varying times over a period of a month were tested simultaneously at a concentration of 10% with five organisms. A marked decrease in response of *L. casei* Texas occurred with increasing age of serum, whereas responses of *Lactobacillus brevis* ATCC 8287 and

[1] This investigation was supported in part by a research grant from the National Cancer Institute, National Institutes of Health, USPHS.

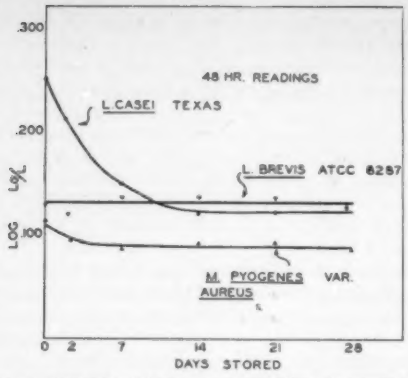

FIG. 2. Response of three assay organisms to serum pools stored for varying times at 4° C and tested simultaneously.

Micrococcus pyogenes var. *aureus* were relatively constant (Fig. 2). In data not shown, responses of two strains of *Lactobacillus arabinosus* (ATCC 8014 and MC-Oklahoma) showed significant decreases with storage, although the effects were somewhat less marked than with *L. casei*.

In a survey of stock cultures, a carefully standardized procedure was used, with one large serum pool stored at 4° C and tested at various times after collection. As shown in Table 1, responses of eight organisms were affected by age of the serum. On the other hand, no effect was observed with two strains of *Leuconostoc dextranicum* (ATCC 8358 and ATCC 8086), *Leuconostoc mesenteroides* ATCC 8293, *L. brevis* ATCC 8287, *Lactobacillus fermenti* Texas, and *M. pyogenes* var. *aureus*. Responses of *L. casei* ATCC 9595 and *Streptococcus faecalis* ATCC 9790 were subsequently shown to be markedly affected by age of serum, but *L. mesenteroides* ATCC 8042 and *Lactobacillus pentoaceticus* ATCC 367 gave equivocal data on repeated experiments.

The mechanism of development of decreased microbiological response on storage of serum is unknown. It is pertinent to note, however, the following findings, obtained principally with the *L. casei* strains at serum concentrations of 10%: (*a*) In studies at 37° C, room temperature, 4° C, and −15° C, *rate* of development of lessened response decreased with decreasing temperature of storage. Similar results were obtained with *Str. faecalis* ATCC 9790 and *L. arabinosus* ATCC 8014. (*b*) The *rate* of development of lessened response in sera from different individuals exhibited rather wide variation. The presence of malignant neoplastic disease caused no distinctive alteration in response patterns. (*c*) Since sera readily "aged" in an atmosphere of natural gas (approx composition:[2] CH_4, 94%; C_2H_6—C_5H_{12}, 5.1%; CO_2, 1.3%; N_2, 0.6%), the phenomenon would appear to be independent of oxygen tension. (*d*) The addition of 0.1% soluble starch did not affect responses of eight sensitive species tested. Since starch has been reported to overcome the toxicity of C_{18} unsaturated fatty acids for at least some bacteria (*2, 3*), an accumulation of such fatty acids from serum lipase activity would appear unlikely. (*e*) Responses to varying proportions of aged serum and fresh serum at a total serum concentration of 10% were more indicative of decrease in nutritive value than of appearance of toxicity during storage of serum. (*f*) Heating fresh serum at 60° C for 30 min had no apparent effect on the rate of development of lessened response on storage at 37° C, although heating did markedly increase the degree of response. Heating stored serum resulted in some increase in response, which did not decrease on further storage. (*g*) Microbiological assays[3] of 17 free amino acids and comparison of paper partition chromatograms[3] of tungstic acid filtrates of fresh and stored pooled sera indicated that the stored serum contained less cystine and more methionine, phenylalanine, and glutamic acid than the fresh serum. However, supplementation with any one of these four amino acids or with a mixture of 16 amino acids did not significantly affect responses to fresh or aged sera.

TABLE 1

72-HR RESPONSES (LOG L_0/L) TO POOLED SERUM AT 10% CONCENTRATION

Organism	Serum stored at 4° C (days)			Basal medium
	0	6	20	
Streptococcus faecalis ATCC 8043	0.082	0.036	0.029	0.032
Str. faecalis Texas	.112	.059	.060	.052
Str. lactis Texas	.109	.066	.070	.053
Leuconostoc mesenteroides Texas	.103	.053	.060	.052
L. citrovorum ATCC 8082	.120	.065	.062	.075
Lactobacillus arabinosus MC-Oklahoma	.207	.131	.117	.060
L. arabinosus ATCC 8014	.184	.130	.110	.063
L. casei Texas	0.280	0.159	0.138	0.035

As stated above, the nature of the substance(s) responsible for the growth stimulation observed with serum was not a primary concern of the present investigation, although we realize that this problem merits attention. The point to be emphasized is that the observed significant effects of storage of serum on microbiological response could conceivably be of importance in many microbiological assays, particularly in view of the probability of storing pooled control serum in the refrigerator until needed. Such stored control serum assayed simultaneously with fresh test sera could yield spurious data and result in erroneous conclusions with regard to the effect of a given factor or condition. In fact, the phenomenon of decrease in growth response on storage of serum was discovered on close scrutiny of an assay procedure which at first sight appeared to show promise in the detection of cancer. Differences obtained be-

[2] Courtesy United Gas Corporation, Houston, Tex.

[3] The authors wish to express their appreciation to Robert Fuerst, of the Department of Biochemistry, who performed these analyses.

tween normal sera and sera from patients with cancer were, of course, attributable to the fact that sera from the cancer cases were assayed shortly after venipuncture and compared with control serum that had been stored in the refrigerator.

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Manuscript received July 23, 1952.

A Study of the X-Irradiation Protection Afforded by Cobalt

W. Parr, T. O'Neill, and A. Krebs

U. S. Army Medical Research Laboratory, Fort Knox, Kentucky

It is generally believed that hemopoiesis is the key to recovery after irradiation injury. Even if this fact does not assure survival of irradiated animals (*1*), it seemed of interest to study the influence of polycythemia-producing substances on irradiation effects. Such a substance is cobalt, which is known to produce polycythemia. The mechanism of this cobalt polycythemia is unknown. It is assumed that cobalt interferes with cellular respiration (*2*), a process of decisive importance again for the magnitude of the irradiation damage. With these facts in mind, investigations on the influence of cobalt in total body irradiation effects were undertaken.

Approximately 400 female Swiss Albino mice (25 ± 1 g) were used. They were divided into four groups for each experiment: group 1 on Purina stock chow diet, group 2 on cobalt diet, group 3 on Purina stock chow diet plus irradiation, group 4 on cobalt diet plus irradiation. The cobalt diet was prepared by immersing the Purina chow pellets in a 2% cobalt chloride solution ($CoCl_2 + 6\ H_2O$) for a 2-min period and then allowing them to dry. The mice were kept on this diet 5 and 8 days before irradiation and for about 15 days after irradiation. Food and water were given *ad lib.*

The mice were irradiated in groups of 10, each group consisting of 5 on Purina chow and 5 on the cobalt diet. The irradiations were done with a Kelley-Koett deep therapy x-ray unit, operated at 200 kv, 6 ma, inherent filtration equiv 0.25 mm Cu, 1 mm Al plus 0.5 mm Cu added, 30 cm target distance, 48 r/min in air; a total of 720 r/air. The mice were observed for 30 days after irradiation, and the mortality rate was recorded every 24 hr.

The results obtained with animals receiving cobalt food for 5 and 8 days prior to irradiation are presented in Figs. 1 and 2. The animals kept on cobalt diet before irradiation show in both cases a significant increase in their resistance against irradiation in comparison to the irradiated groups on Purina chow only.

The general appearance of the cobalt-fed irradiated animals was quite similar to that of the nonirradiated animals. They exhibited smooth fur and normal vitality, whereas the irradiated animals on normal food and the few animals that died in the cobalt-fed irradiated group showed all the signs of heavy irradiation damage. To obtain the beneficial effect the weight of the animals, the preparation of the cobalt food, and ease of accessibility to food and water are of decisive importance.

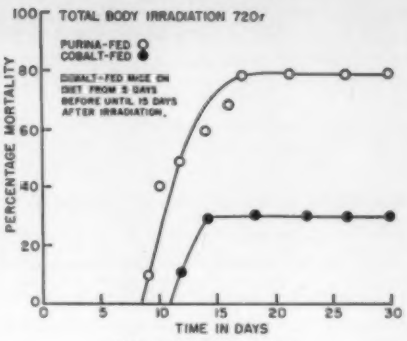

FIG. 1. Mortality rates.

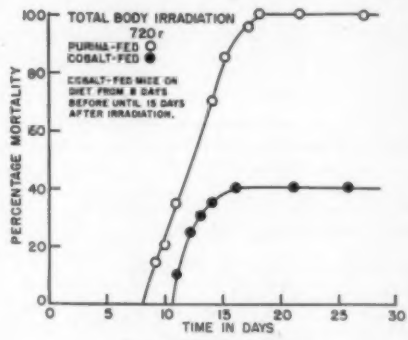

FIG. 2. Mortality rates.

The protective effect exhibited by cobalt lends itself to discussion and comparison with present irradiation protection investigations.

An oxygen deficiency increases the resistance against irradiation damage (*3, 4*). Compounds such as cysteine and glutathione counteract irradiation effects on sulfhydryl enzymes (*1, 5*). The proper support of the hematopoietic system stimulates and speeds recovery (*6, 7*). In cobalt administration experiments, similar processes are going on. According to Barron and Orten (*8, 9*), cobalt interferes with cellular respiration and produces anoxia. According to Burk *et al.* (*10*), cobalt may block sulfhydryl groups and perhaps other groups necessary for tissue metabolism. According to Orten (*9*), cobalt produces a strong polycythemia, indicating an active stimulus to the hematopoietic system.

Which of these mechanisms is decisive in the ob-

served cobalt protection effect remains to be investigated. It may be that not one mechanism alone but all three together, working in a functional correlation, produce the effect. The parallelism is so close, and the possibilities of obtaining more information on certain phases of the protection mechanics are so obvious, that further investigations are indicated.

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Collection and Storage of Chicken Plasma for Tissue Culture

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Since Carrel and Burrows introduced the use of chicken plasma in tissue cultures, many attempts have been made to replace it by something more readily available, such as agar (*1*), cellophane (*2*), or commercial thrombin and fibrinogen (*3*). These agents have proved fairly successful in the hands of their sponsors, but generally speaking the chicken plasma clot is still the most satisfactory substrate for tissue culture.

It has been said that experienced operators seem to draw blood without difficulty by intuition rather than by method. We hope that the method here described will be of help to the inexperienced and simplify the procedure for the experienced. Steps eliminated in the collection of plasma are based on our observations and are supported by information obtained from a survey of nine tissue culture laboratories.

Bleeding methods. Carrel and Burrows (*4*) in 1911 recommended collecting blood from the carotid artery by "the method similar to one used by Delezenne and by Gengou" (no reference given). The bird is etherized, and the carotid artery is exposed. The vessel is rubbed with dry gauze and covered with olive oil. A glass cannula sterilized in olive oil is used to run the blood into chilled paraffin-coated tubes, and after centrifugation plasma is removed with paraffin-coated pipettes. This is a delicate and time-consuming operation and is used in only three of the nine laboratories that we surveyed.

In 1928 M. R. Lewis (*5*) introduced the cardiac puncture method, using a lateral approach. This simplified the procedure but introduced the need for an anticoagulant. No toxic effects are observed when heparin is used, and six of the nine laboratories surveyed use this method.

The survey confirmed our observations on the following points:

1) Fasting is not essential to collection of clear plasma and does not affect clotting quality of blood. The fat content of chicken feed is not high enough to result in chylous plasma. Overnight fasting, however, is advantageous in the interclavicular approach to the heart. A full crop might get in the way. Fasting also eliminates unassimilated digestion products from the circulation. (One laboratory bleeds without fasting.)

Fig. 1. Bird in position for bleeding.

2) Paraffin coating of tubes and pipettes is unnecessary; the important thing is to keep them well chilled. Three laboratories use plain tubes; one collects in plain tubes but stores in paraffin-coated tubes; five use paraffin-coated tubes.

Modified MacArthur (6) technique of collecting blood. Briefly, this is a cardiac puncture method of reaching the heart through the interclavicular space. The Pavlech modification uses the same approach, but the blood is collected in tubes instead of in a syringe.

Birds selected for bleeding should be 10–12 months old, as management of the bird is easier and the

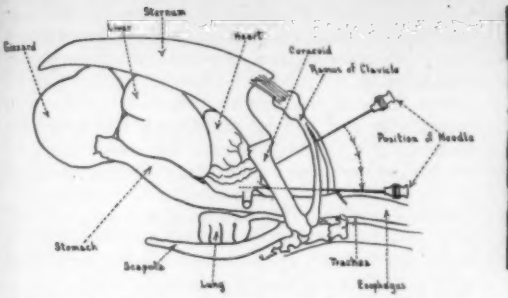

FIG. 2. Diagram showing location of heart and position of needle.

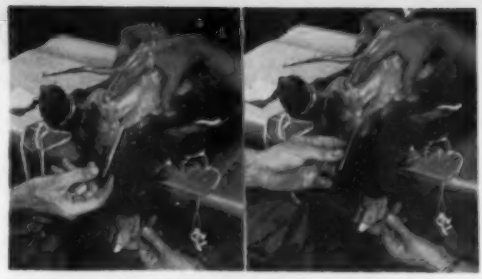

FIG. 4. Undraped bird: collecting the blood.

plasma yield is more adequate. Plasma from older birds is supposed to contain growth-inhibiting factors.

In preparing the bird for bleeding the feathers in the clavicular area are plucked and trimmed to present a clean field of operation. The bird is then placed on its back on a board $\frac{3}{4}'' \times 14'' \times 18''$ with U-shaped bolts or hooks at each corner. Two-inch bandage or muslin ties are used to immobilize the bird. The head hangs over the edge of the board and the operating table (Fig. 1). The bird remains remarkably quiet in this position throughout the operation, without anesthesia. The amount of jerking toward the end of bleeding is no more than that observed under anesthesia.

After proper disinfection of the skin the bird is draped for aseptic operation. The operator uses a 15- or 16-gauge 3- or 4-in. needle (depending on the size of the bird) attached to a 1-cc tuberculin syringe. The syringe aids in keeping the hub of the needle sterile while the heart is being located. There is no need to rinse either the needle or the syringe with olive oil (Figs. 2, 3).

Before starting the operation, the triangular opening to the thoracic cavity formed by the coracoid bones and the neck is palpated. The needle is inserted in the median plane, approximately ½ in. below the angle formed by the clavicle and is directed downward at approximately a 45° angle until the point of the needle is in the dorsal angle (ventral when the bird is standing) formed by the coracoid bones. Then the syringe is lowered until it lies approximately ½ in. above the neck, and the needle is pushed inward and upward 2°–5° through the interclavicular space until the heartbeat is felt. The heart is penetrated, and at the same time slight negative pressure on the syringe is maintained. As a rule, blood will appear with sufficient force to push back the plunger. The syringe is then removed from the needle and the first milliliter collected is discarded along with the syringe to avoid contamination with tissue juice. In a successful operation blood flows rapidly through the needle and is collected in 10–12 ml amounts in chilled tubes (Fig. 4). Should a clot form in the needle before bleeding is completed it can be pulled out with a pair of fine forceps and bleeding continued. Each tube must be corked and placed immediately in a bowl of ice chips. The amount of blood collected depends on the size of the bird.

Collection and storage of plasma. After the blood has been completely chilled the tubes are placed in chilled carriers, carefully balanced, and centrifuged at about 2500 rpm for 8–10 min. After centrifugation the plasma is pipetted into chilled tubes and stored at 5° C. The crucial point in collecting chicken blood for plasma seems to be the immediate chilling of the blood. It is possible that chilling blocks the clotting mechanism, which is released upon the addition of tissue extract. Once "blocking" has taken place the plasma remains fluid under ordinary refrigeration.

Tightly corked tubes of plasma will keep at 5° C for 4–6 months. For longer storage it is best to lyophilize it. Sometimes stored plasma will gel. This is different from a plasma clot, in that the plasma can be thinned out with an equal amount of Tyrode solution; a satisfactory clot forms when tissue extract is added to it.

FIG. 3. Lateral views; dissected bird shows position of the heart and needles.

Advantages of bleeding by the interclavicular approach to the heart are: (1) simplicity of operation; (2) fractional collection of the blood insures against loss of all the blood by clotting; and (3) the use of anticoagulants is eliminated.

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Vegetative Propagation of Mango (*Mangifera indica* L.) by Air-Layering (*Gootee*)

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Mango is one of the most popular fruits of the tropics and subtropics; and it is definitely the best fruit of India, where it commands the largest acreage of any single fruit crop. At present it is propagated commercially by inarching, or "approach grafting," on seedling stocks of unknown heritage. There has been a long-felt need for the exploitation of clonal root stocks in the cultivation of mango, because it will not only help in standardizing the innumerable mango varieties, but will also enable the multiplication of desired fruit plants. The situation was similar in apple orchards in temperate countries until Hatton (*1*) selected a few types of root stocks of known performance, with a view to eliminating variations in apple varieties. These root stocks produced dwarf, semivigorous, or vigorous trees as desired and are now very extensively used in apple orchards practically all over the world.

In the case of mango, however, the exploitation of such known root stocks, even if they were selected, was rendered impossible until now, as no method was available to multiply them vegetatively. Guha-Thakurta and Dutt (*2*) attempted vegetative propagation of mango by cuttings and *gootee*. They got promising results when the trees were quite young—i.e., 2 or 3 years old—but failed in air-layering shoots or rooting cuttings from older trees. Gardner and Piper (*3*) reported 31% success in rooting mango cuttings from one-year-old seedling plants but negative results from older plants. Said and Shoushan (*4*) succeeded in rooting mango cuttings, but these shriveled up later on and died. Whatever success has been achieved in rooting cuttings or shoots from young plants is of very little practical importance, as it provides only a limited number of plants and will hardly serve any purpose for clonal root stocks since the tree will not have been observed for its vigor and fruiting performance. In the present work attempts were therefore made by the author to propagate selected mother plants with the help of well-known root-producing hormones. Six hundred vigorous 2-year-old shoots, 1.5 cm in diameter, were selected from 30-year old trees of two vigorous varieties of mango—Samarbahist Alibag and Gopalbhog. The selected shoots were 18"–24" long, and for layering a ring of bark about 1" in width was removed. The exposed wood was scraped off with a knife to remove the cambium cells, if any.

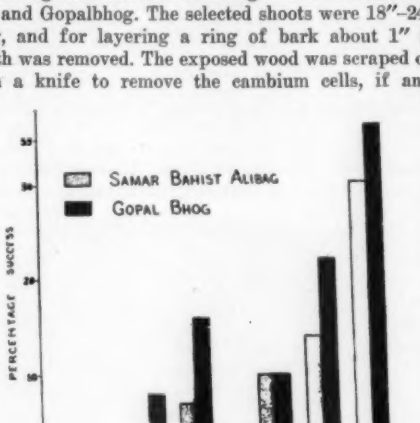

Fig. 1. Effect of hormones on rooting of mango shoots.

Two hormones—α-naphthalene acetic acid and β-indolacetic acid—were then applied to the upper edges of the bark, in three concentrations, 0.25%, 0.5%, and 1.0%, in lanolin paste. The ringed surface was then covered with wet sphagnum moss and wrapped securely with hessian cloth. The shoots were treated in June 1950. Fifty shoots of each variety were thus treated with concentrations of the hormones given above. Roots were formed in 45–60 days, when shoots were detached from the mother plant and potted. Results of these treatments are shown in Fig. 1.

These plants have been established in the field as mother plants for the past 2 years and have taken well. It is evident that shoots from older mango trees can be air-layered quite successfully. Of the two hormones tested, α-naphthalene acetic acid gave better results than β-indolacetic acid. Higher concentrations of both acids proved better than lower ones. The latest view in rooting mango cuttings or shoots was that of Gardner and Piper (*3*), who believed that its success is linked with the juvenile stage of the plant, which varies from species to species. Results reported in this paper clearly prove, however, that mango shoots can be air-layered successfully from quite old mother plants, provided the shoots are in active physiological condition and the right concentration of hormones is applied to them.

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Unusual Reproductive Phenomena in Rodents

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It was observed while breeding white rats and mice for experimental purposes that occasionally a female would deliver two successive litters without having been bred a second time. It has been the practice of the author to segregate pregnant animals in brood cages from the time they were obviously pregnant until the young were of weaning age. Over a period of years, three unequivocal cases of this phenomenon have been personally observed. One recent example of anomalous pregnancy in a guinea pig is also included.

Case I: White rat Y, female, was caged with two males. On Sept. 18, 1940, female was isolated because of obvious pregnancy. On Sept. 20, 8 healthy young were born, all of whom survived. On Oct. 15 this same rat gave birth to another litter of 11 young. The first litter was between 3 and 4 weeks old at this time and was removed from the cage. Of the second litter, 5 were dead at birth, 4 died before weaning age, and 2 lived. Twenty-five days intervened between the successive litters. This female rat had been separated from all other rats two days before the first litter was born, and from all but her own young for 27 days before the birth of the second litter. The remaining history of this animal was uneventful, although she survived to July 15, 1941, when she was sacrificed.

Case II: The author has personal knowledge of this animal, and it is presented on personal communication from A. Barber (*1*). Mouse L-7, *dba* female, and her own young, L-16 (male) and L-15 (female), were accidentally allowed to remain together until the young were mature and mating occurred. On July 29, 1950, each animal was isolated, and on Aug. 8, L-7 delivered 6 normal young. On Sept. 1, 24 days later, the mother was isolated, and on Sept. 3 she delivered 7 normal young. This mouse had not been mated since July 29, or 36 days before the birth of the second litter. The mice in both litters were *dba*, and of mixed sex.

Case III: Deer mouse (*Peromyscus maniculatus gambelii*), brown, adult, female was isolated Dec. 18, 1950, because of pregnancy. On Dec. 27, 2 young, about 1 week old, were found when the cage was changed. On Jan. 15, 1951, 4 newborn young were found when the cage was changed on this date. Four days later the older mice, 1 male and 1 female, were removed. The second litter had velvety coats, but one was a runt that subsequently died. The survivors of this litter were 2 females and 1 male. The time between isolation of the mother and birth of the second litter was 28 days, and the time between the birth of the first and second litters was 24–26 days. The *Peromyscus* female was observed for 9 months after this, but no unusual behavior was noted. Observation of these animals is more difficult than with other mice because of their shyness and their burrowing habits.

Guinea pig: Albino female, bred to an albino male, had previously had two pregnancies. The week of Apr. 14, 1952, this animal was isolated because of pregnancy, and during the week of May 12 she delivered 4 healthy young. She was placed with two other sows and their young (3–4 weeks old) when her litter was about 2 weeks old, because of a housing emergency. She was left in this cage for less than 24 hr. None of the other pigs were albinos, but on June 27 this animal gave birth to 3 healthy, well-developed, albino female young. The time between the birth of these two litters was 42–46 days, and the interval between the time she was isolated and the birth of the second litter was 70–74 days.

Two phenomena have been reported to occur in mammals, including rodents, which involve irregularities in pregnancy. One of these, delayed implantation of the blastocyst stage, was reported and reviewed by Hamlett (*2*). This occurs normally in certain animals, and irregularly in others, including rats and mice, according to him. However, if delayed implantation is the explanation of the three cases (one rat and two mice) reported here, the blastocysts must have survived during some portion of the first pregnancy, been retained in the uterus during delivery, and been implanted following delivery of the first litter.

The second phenomenon, superfetation, has been reviewed by Rollhäuser (*3*), who reported a case in a mouse. The essential indication that this has occurred is the delivery of a second litter at a shorter interval after the first than the normal gestation period. Rollhäuser found reports of time intervals from 7 to 16 days between the birth of the two litters in rats and mice. It seems unlikely that this is the explanation of our rat and mice cases, as the time intervals between litters in these animals was longer than the normal gestation period. The case of the guinea pig may well be an example of superfetation, however, since the time interval between the delivery of the two litters was much shorter than the minimum gestation period for guinea pigs, according to Ibsen (*4*). Another argument in favor of superfetation in this case is that the time interval between the isolation of this animal and the birth of the second litter (70–74 days) coincides with the maximum gestation period reported by Ibsen.

It is possible that a combination of superfetation late in pregnancy, combined with delayed implantation of the blastocysts, may account for the observed results. However, the case of the *dba* mouse is difficult to explain on this basis, inasmuch as 10–15 days must have intervened between the last possible mating and the implantation of the blastocysts. Parthenogenesis is improbable because at least two of the last litters were made up of male and female animals.

This phenomenon may be more common than the literature would indicate. Two people who breed animals for experimental work have told the author that they have observed it occasionally, but did not have adequate records on individual animals. The only reference the author has been able to find of such cases is the one by Burrows (*5*), who reports ten examples in Wistar rats and two in *dba* mice. Five of these animals had records of the date of isolation, and in these cases the intervals between isolation and the birth of the second litter were 24–29 days. Burrows quotes two references to this phenomenon which he found in the literature, involving two cases in mice and one case in a rabbit. This anomalous type of pregnancy is not confined to any one genus, having been observed in the cases reported here, in *Rattus, Mus,* and *Peromyscus* (*6*). It is not confined to highly inbred strains, as the *Peromyscus* mouse was one of a stock carrying both white coat color and hairlessness, apparently as recessive characteristics.

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The *in Vivo* Conversion of Glycine to Serine

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The conversion of glycine to serine by the liver has been shown to occur *in vitro*. A similar reaction has not been previously demonstrated in the liver of the intact animal. It will be shown that under varying conditions the metabolic path of glycine in the liver of the intact mouse is similar to the *in vitro* reaction.

Nine "A" strain male mice were equally divided into three groups. Group I was supplied with its normal diet, Group II was given only a saturated solution of glucose in water, and Group III was allowed only water. This diet was continued for 72 hr.

Each mouse was then injected with 1.728 mg of glycine-2-C^{14} (8.6 μC) of C^{14}-methyl-labeled glycine, and one mouse from each group killed with ether 2, 4, and 6 hr after the administration of the radioglycine.

TABLE 1

Group	Time (hr)	Amino acids	Relative radioactivity
I (Normal diet)	2	Glycine	++++
	4	"	++++
		Serine	++++
	6	Glycine	++++
		Serine	++++
II (Glucose + water)	2	Glycine	++++
		Serine	++
	4	Glycine	++++
		Serine	+++
	6	Glycine	++
		Serine	++
III (Water alone)	2	Glycine	++++
	4	"	+++
		Cystine	+
	6	Glycine	+++
		Cystine	+
		Serine	+++

The liver was removed *in toto* from each animal and hydrolyzed in 6 *N* HCl over a steam bath for 18 hr. The hydrolysate was filtered, and salts were removed by ion exchange technique. The solution was concentrated and chromatographed two-dimensionally on No. 1 Whatman filter paper (*1, 2*), using phenol and butanol propionic acid. After the papers had dried, they were radioautographed on Eastman No-Screen x-ray films. The amino acids on the chromatograms were then developed with a spray of 0.1% alcoholic ninhydrin. By superimposing the respective radioautographs on the developed chromatograms the radioactive amino acids could be determined. This activity must have been derived from the injected radioglycine. A small fragment of each liver was also examined microscopically to determine any cytological changes that were due to diet.

Table 1 summarizes the results. Two hr after injection, only the glucose-fed animal produced a moderate amount of radioactive serine. After 4 hr the glucose-fed animal had produced a little more radioserine, and in the normal-fed animal radioglycine and radioserine were present in approximately equal concentrations. Only after 6 hr did the water-fed animals convert glycine to serine. In addition they showed the presence of a small amount of radiocystine not present in either of the two other groups.

Liver biopsy revealed no abnormality in the normal group, minimal vacuolization was present in the glucose-fed animals, and marked degenerative changes were seen in the water-fed group.

Winnick et al. (*3*) showed that after incubation of liver homogenate with C^{14}-labeled glycine, 60% of the isotopic carbon was found in serine. Sakami (*4*) felt that such conversion occurred by means of the combination of glycine with formate and provided

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evidence that glycine itself was a major source of the formate. Siekewitz and Greenberg (*5*) confirmed Sakami's work and also showed that the liver uptake of methyl-labeled glycine was 1½ times as fast as that of carboxyl-labeled glycine.

The results of this experiment show that the intact liver of mice handles parenterally administered glycine as it does *in vitro*. It is of interest that even the grossly damaged liver of depleted animals behaves similarly, although the conversion is slower and there is the suggestion of an additional metabolic path in the production of radiocystine.

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Identification of Murexine as β-[Imidazolyl-(4)]-Acryl-Choline

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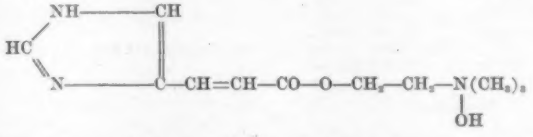
Murexine is an active product contained, often in very large quantities, in the median zone of the hypobranchial body of *Murex trunculus* and of other related species of mollusks. Biologically, it manifests intense nicotinic and curariform actions; chemically, it is a choline derivative.

We had already come to these conclusions some years ago, following our first researches carried out on various pure salts of murexine (picrate, picrolonate, flavianate, styphnate, and reineckate) (*1, 2*).

Further investigations, a preliminary account of which is given in the present paper, have enabled us to clear up the chemical constitution of murexine, and consequently to identify this substance as β-[imidazolyl-(4)]-acryl-choline or urocanyl-choline.



Murexine
(Urocanyl-choline)

Murexine picrate, the starting material of all our researches, is urocanylcholine dipicrate (UCD).

Characteristics of murexine picrate: More or less elongated plates and thin crossed needles, slightly soluble in cold water (less than 0.1%), much more so in boiling water, from which the product may be easily recrystallized; mp 218°–221° C, with decomposition.

(UCD) $C_{11}H_{12}O_2N_2 \cdot C_6H_6O_7N_3 \cdot C_6H_2O_7N_3$ (681)	Calc:	C 40.53;	H 3.35; N 18.50%
Murexine picrate (Sample 1)	Found:	40.68	3.57 18.34%
" " (Sample 2)	"	40.55	3.60 18.71%
" " (Sample 3)	"	40.51	3.60 18.70%

Percentage of picric acid in murexine picrate was determined quantitatively by direct weighing, and by the nitron method according to Busch (*3*). In the direct weighing method, aliquots of 1–4 g of murexine picrate were treated in a boiling water bath with 30–100 ml of 1 *N* HCl for 1–2 hr. After the product was completely dissolved, the solution was cooled and extracted with ethyl ether in a Palkin automatic extraction apparatus, until the solvent removed no more picric acid, and the liquid in the extractor tube had become colorless. The intensely yellow-colored ether in the extraction flask was evaporated, and the residue, consisting of pure picric acid (mp 121.5°–122° C), was weighed.

Picric acid from UCD Calc: 67.26%
Picric acid from murexine picrate
Found: 67.70%–67.10%–67.30%

In the nitron method, the determinations, also gravimetric in this case, were performed on aliquots of 0.2 g of murexine picrate, dissolved in 60 ml of hot water.

Nitron picrate from UCD Calc: 158.6%
Nitron picrate from murexine picrate
Found: 158.4%–157.8%–160.4%

Murexine hydrolysis products. The positivity of the Feigl hydroxylamine reaction (*4*) confirms that murexine is an ester of a carboxylic acid. The substance saponifies quickly in alkaline medium, more slowly in acid medium (heating in boiling water bath for 1–2 hr with 1 *N* HCl), liberating choline (I) and the acid which esterifies choline (II).

For various reasons the acid hydrolysis was preferred. After the picric acid was quantitatively removed with ether and the acid aqueous liquid was evaporated to dryness, there remained a white deposit, rather hygroscopic, which was brought to constant weight over phosphorus pentoxide *in vacuo*.

From two aliquots of 1 g each of murexine picrate, 476 and 467 mg of material were obtained.

$C_5H_{11}ON \cdot Cl$ (I) + $C_6H_4O_2N_2 \cdot HCl$ (II) Calc: 46.11%
from UCD

[1] We are indebted to, and wish to thank, F. Canal, of the Farmitalia Research Laboratories, for the elementary analyses, and K. Bernhardt, of the Biochemical Department of the University of Basel, for a sample of synthetic urocanic acid.

Choline (I). The presence of choline among the hydrolysis products of murexine was ascertained chemically (preparation of a reineckate identical to that of choline), by paper chromatography (*5*), and pharmacologically (the acetylation of the murexine hydrolysis products gives a substance which cannot be distinguished from acetylcholine).

Choline was determined quantitatively by direct weighing, following its precipitation as Reinecke salt. Aliquots of 200 mg of murexine picrate were used in the determinations.

$C_5H_{14}ON \cdot C_4H_7N_6S_4Cr$	from UCD	Calc: 61.97%
	" murexine picrate	Found: 62.80%–62.85%
$C_5H_{14}ON \cdot C_4H_7N_6S_4Cr$		Calc: Cr 12.26%
Reineckate from murexine hydrolysis products		Found: 12.46%
" " choline chloride		" 12.44%

Choline esterifying acid (II). Having demonstrated that murexine picrate contained 2 molecules of picric acid and 1 of choline, we were compelled, on the basis of the elementary analyses, to acknowledge the presence of 2 nitrogen atoms in II. Owing to the positivity of the Feigl reaction, also, the presence of 2 oxygen atoms became extremely probable.

A decisive step forward in the identification of product II was made by observing that it gave, in alkaline medium, an intense coupling reaction with diazonium salts, above all with the Pauly reagent. The color reactions of phenols, indoles, purines, and pyrimidines were, on the contrary, negative (these substances were also excluded through the ultraviolet spectrophotometric analysis). On the basis of these findings our orientation toward an imidazole derivation of the substance became more and more justified.

Chromatography on paper enabled us to discard the identification of product II with β-[imidazolyl-(4)]-propionic acid, and definitely to establish its identity with β-[imidazolyl-(4)]-acrylic acid, a possible intermediate product of the histidine metabolism.

A complete and easy separation of the choline chloride from the hydrochloride of the β-[imidazolyl-(4)]-acrylic acid was brought about by chromatographing the murexine hydrolysis products on a column of Whatman cellulose powder. *n*-Butanol saturated with 1 *N* HCl was used as solvent.

The hydrochloride of the β-[imidazolyl-(4)]-acrylic acid was finally transformed into the β-[imidazolyl-(4)]-acrylic acid, which is much less soluble in water and therefore more easily crystallizable and purifiable.

Needles, mp 217°–218° C, mixed mp with synthetic urocanic acid 217°–218° C.

$C_6H_6O_2N_2 \cdot 2H_2O$ (174)	Calc:	41.17	H 5.88	N 16.47%
Hydrolysis product II	Found:	41.25	5.93	16.41

β-[Imidazolyl-(4)]-acryl-choline dipictrate has been recently obtained by synthesis in our laboratories (*6*). It is identical with murexine picrate, both from the chemical and the pharmacological point of view.

Extensive pharmacological researches are now in progress on murexine and similar synthetic substances.

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The Effect of Estrogen on the Isometric Tension of Rabbit Uterine Strips

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It has been shown in our laboratory (*1*) that the concentration of uterine actomyosin, the contractile protein of the myometrium, is under the control of the ovarian estrogenic hormones. When rabbits in natural estrus were subjected to bilateral ovariectomy the concentration of uterine actomyosin decreased to about one fifth the original estrous value. This extreme condition could be reversed, however, by the administration of estrogen to the living animal, which brought about gradual increase in actomyosin concentration toward the estrous value.

Previous observations (*2, 3*) also indicated that similar changes in the concentration of uterine actomyosin occur under physiological conditions (pregnancy, labor, and menopause) that involve alterations in the estrogen output of the animal's own ovaries.

It has been generally accepted and has become a textbook statement that the fibrous protein actomyosin is the final contractile substance of muscle. The direct evidence in support of this conclusion—namely, Szent-Györgyi's actomyosin-thread "contraction" phenomenon—has not been accepted by some authors (*5, 6*). Evidence, however, may be obtained indirectly by utilizing the above-mentioned experimental variability of actomyosin concentration in uterine muscle. One would expect that the concentration of the final contractile substance would determine the maximum force the muscle is able to develop, provided that conditions are otherwise optimal. The existence of such a relation between actomyosin concentration and maximum tension will be demonstrated if the former is varied in a given muscle and proportionate alterations in maximum tension are then observed.

In accordance with this postulate we have measured the maximum tension developed by freshly excised uterine strips *in vitro* under controlled hormonal conditions in which the concentration of uterine actomyosin had previously been determined—i.e., in natural estrus, after ovariectomy, and ovariectomy followed by estrogen treatment.

Since previous experiments have clearly shown that in these hormonal conditions the spontaneous rhythmicity of myometrial contraction varies greatly *in vivo* (*7*), as well as *in vitro* (*8*), owing to the effect of estrogen, optimal electrical stimulation was used in our experiments in order to secure comparable conditions.

Purebred mature virgin female New Zealand white rabbits were used. Under Nembutal anesthesia the uterine horns were rapidly removed and placed for 10 min in oxygenated mammalian Krebs solution at 0° C. During this time the muscle fully relaxes and remains relaxed. Longitudinal strips of standard length (25 mm) and about 12 mm wide, were cut and placed in a glass tube filled with Krebs solution between two platinum hooks, by which they were attached to the writing lever of an isometric tension recorder. The temperature (37.5° C), the oxygen concentration (2.0 vol%), and the pH (7.4) were kept constant. A previous study with respect to optimum electrical stimulation taught us that stimuli of 5-sec duration, 24 v, 60-c AC, should be used (*9*). Alterations in the voltage (25%) or in the duration resulted in submaximal tension. Moreover, this type of stimulation at optimal frequency of one or two stimuli per minute produced contractions of uniform maximum tension for any desirable length of time.

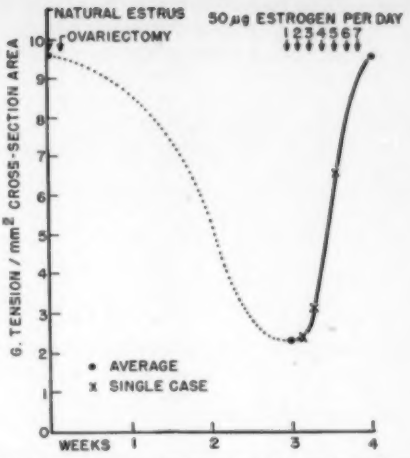
NATURAL ESTRUS
OVARIECTOMY
50 μg ESTROGEN PER DAY
1 2 3 4 5 6 7
G. TENSION / mm² CROSS-SECTION AREA
0 1 2 3 4 5 6 7 8 9 10
• AVERAGE
x SINGLE CASE
WEEKS 1 2 3 4

FIG. 1. The effect of estrogen on the maximum isometric tension of rabbit uterine strips *in vitro*.

SE)/mm² cross-section area. The muscle, as reported previously, contains 7.6 mg actomyosin/g tissue in this condition. Three weeks after bilateral ovariectomy the tension drops to an average figure of 2.3 g (± 0.41 SE). The actomyosin concentration was found to be 1.7 mg/g tissue in this condition. Taking the estrous and the castrate conditions as extremes, the ratio of tension in the two contrasting states is 9.6/2.3 = 4.2, and that of actomyosin is 7.6/1.7 = 4.5. Considering the great difference between the two kinds of measurements, the two figures appear to be in good agreement.

TABLE 1

THE EFFECT OF ESTROGEN ON THE MAXIMUM ISOMETRIC TENSION OF RABBIT UTERINE STRIPS *in Vitro**

No.	Treatment	Tension	No.	Treatment	Tension	No.	Treatment	Tension
22	Natural estrus	8.00	2	Ovariectomy	2.00	6	540 μg E/ 7D	5.65
23	" "	7.80	4	"	0.70	7	560 μg E/ 8D	6.70
24	" "	14.20	12	"	4.30	8	600 μg E/ 9D	6.72
25	" "	10.03	13	"	1.00	17	450 μg E/ 9D	12.40
43	" "	7.70	14	"	1.18	18	500 μg E/10D	7.35
Av		9.60	15	"	1.49	19	600 μg E/12D	14.70
			37	"	3.40	40	350 μg E/ 7D	12.82
			38	"	3.10	41	350 μg E/ 7D	13.40
			39	"	3.60	42	350 μg E/ 7D	6.30
			Av		2.30	Av		9.55
			28	5000 μg P/5D	2.96			

* Tension calculated in g/mm² cross-section area of uterine muscle used for determination. E = estrogen, P = progesterone, D = day.

After the maximum tension was determined the effects of ovariectomy and of estrogen administration were recorded from histological sections, and the cross-section area of muscle used was measured. Thus each value reported represents maximum tension per square millimeter of cross-section area.

As shown in Table 1, the average maximum tension of uterine strips from estrous rabbits is 9.6 (± 1.11

If, 3 weeks after castration, estrogen is administered in 50 μg daily doses for at least 7 days, the original estrous value of maximum tension is obtained (9.55 g ± 1.11 SE). As already mentioned, actomyosin increases in a similar fashion following estrogen treatment.

If, instead of estrogen, the other ovarian hormone, progesterone, is administered to the ovariectomized

rabbits, no significant change occurs in tension. Similarly, if estrogen and progesterone treatments are combined, the maximum tension of the uterus will not be significantly different from that in animals which were treated with estrogen only. This observation is in agreement with previous findings that progesterone domination does not significantly alter the actomyosin concentration (*10*).

Fig. 1 indicates the course of gradual increase in maximum tension as a result of the administration of estrogen. The curve is S-shaped. The increase in actomyosin concentration is also slight during the first few days of estrogen treatment (observations on this point were carried out only up to 4 days of estrogen treatment).

These observations indicate that the maximum isometric tension developed by the uterus depends in a final sense on the concentration of actomyosin, and thus the term "contractile protein" seems to be adequate.

In conclusion, we wish to emphasize the singular behavior of uterine muscle with respect to estrogen, which is characteristic, so far as known, of no other muscle. The final contractile system being dependent upon this specific hormone, we are able to make it disappear and reappear again in a fully grown animal as many times as the experiments require. Changes in actomyosin concentration in skeletal muscle related to hormone levels or other physiological conditions have not as yet been observed, except during the process of embryonic development, and no means is known of causing regeneration of the final contractile system in skeletal muscle once it has degenerated. It is a noteworthy fact, therefore, that we have in the uterus a tissue in which the actomyosin concentration can be changed at will for the purpose of observing simultaneous alterations in function. This tissue may be a useful experimental material for more general studies than ours. It can be considered, for example, for studies in growth and protein synthesis.

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Comments and Communications

Un-American Activity

We have noted with misgiving the continuation of attacks by a Congressional committee, individual members of Congress, and certain journalists upon the reputation of the new President of the American Association for the Advancement of Science, E. U. Condon, and indeed upon the American Association for the Advancement of Science itself. May we take this opportunity to express our vigorous disapproval of such attacks, and our concern about the political climate which makes them possible?

We wish also to commend your organization and its officers for their long history of active championship of the cause of scientific freedom.

The American Society for Pharmacology and Experimental Therapeutics, Inc.
Carl C. Pfeiffer, *Secretary*

Chicago, Illinois

Pain—Controlled and Uncontrolled

The stimulating article by Henry K. Beecher, entitled "Experimental Pharmacology and Measurement of Subjective Responses" (Science, **116**, 157 [1952]), seems to us to require some extension. It is important to avoid overemphasis upon a single aspect of the study of pain; to wit, action of analgesic agents. Such studies, although of recognized practical importance, are not broad enough to encompass the analysis of the total pain experience.

We enthusiastically endorse Beecher's thesis that man's *subjective response must be used* for the study and the evaluation of pain sensation. It is perhaps a truism to say that one cannot study pain by avoiding it, yet methods of study that are directed at obtaining "objective data" about pain are nearly always experiments that attempt to avoid the *sine qua non* for pain studies—the sensation of pain itself. Beecher unfortunately falls into this trap and contradicts himself by saying in his article that "the chief field of usefulness for experimental pain methods may be in animals," after having emphasized that pain must be evaluated by the subjective response in man.

We consider arbitrary and confusing Beecher's emphasis on the dichotomy "experimental" pain—that produced by measured noxious stimuli in the laboratory—and "real" or "pathologic" pain—such as postoperative wound pain. He states that he has developed a successful method for the study of the latter, but implies that no one has been able to study "experimental" pain successfully and to relate such studies to the suffering patient.

In our monograph *Pain Sensations and Reactions* (Baltimore: Williams & Wilkins), we define the "pain

experience" as the individual's integration of all the effects of noxious stimulation and pain. These include (*a*) reactions to the threat of pain prior to actual contact with a noxious stimulus; (*b*) reactions to the noxious stimulation, locally at the site of stimulation, and at the cord and brain stem level (segmental), where integration of important responses begins—i.e., flexor reflexes, neurohumoral, cardiovascular, and other responses; (*c*) the sensation of pain itself, which is integrated at suprasegmental levels, together with accompanying sensations such as pressure, fullness, warmth, cold, etc.; and (*d*) reactions to pain sensation, as, for example, in certain religious rites and in behavior patterns involving masochism and sadism.

These responses are closely interdependent, and it is obvious that pain sensation itself is only a part of this constellation and bears somewhat the same relation to it that vision does to graphic art. It would be only the extreme aesthete who would insist upon limiting the study of vision to the art gallery. *Pain sensation must be separated from associated reaction patterns* if progress is to be made, which Beecher recognizes and then waives.

It is not of basic importance as regards the production of pain whether tissue damage results from specific types of stimulation used in the laboratory or from a surgeon's scalpel. But it is extremely relevant to the individual's pain experience, and the investigator must appreciate which aspect of this experience he is interested in exploring. The study of pain sensation *per se,* never easy, can often be most profitably pursued when the implications of the pain are not a major factor, as, for example, when the thermal radiation method is used. Pain *sensation* is far more difficult to investigate when an individual is extremely frightened, inattentive, obtunded, prostrated, "sick," or exhausted. On the other hand, these would be ideal circumstances for the assay of an agent designed to make the patient "more comfortable." The bedside method is the only one that will ultimately establish whether a given analgesic has a place in clinical medicine. On the other hand, the separately studied effects of an agent on the pain threshold, pain intensity, and reactions to noxious stimulation, local and general, are of vital interest to the investigator and therapist.

Beecher has a system of careful controls for testing analgesics at the bedside and through statistical analysis has been able to rate the effectiveness of various agents in producing postoperative comfort. For postoperative purposes it is important and sufficient to know that, after a given operative procedure, a chemical agent can make the patient more comfortable and afford sleep. Such data, however, are nonspecific; hence their usefulness is at best limited. For example, it cannot be assumed that the information obtained from postoperative pain will apply equally well to pain of labor.

In short, Beecher holds that "pathologic" pain be studied as a unitary phenomenon, whereas in our laboratory and clinical studies there have been developed methods for ascertaining pain threshold, assaying pain intensity, defining pain quality, and appraising reactions to pain. The effects of analgesics upon these variables have been described. In addition, the nature of the adequate stimulus for pain has been clarified—i.e., the production of destructive reactions in tissue at a rate above the ability of the cell to compensate. It would thus appear to be a mistake for investigation to be limited to a single approach to so complex an experience as that of pain. Rather, new and vigorous attacks should be made on the problem at different levels, keeping in mind always that answers obtained by each such attack will throw light upon only a few aspects of the pain experience. It may be argued that a synthesis of these separate components into the "pain experience" is difficult, but the practical importance to the physician in controlling the various aspects of the pain experience is unquestioned.

Finally, we feel compelled to comment upon Beecher's failure with the thermal radiation method for measuring pain threshold in obtaining satisfactory measurements of pain threshold-raising action following administration of analgesics. He states that in his laboratory he "was completely unable to differentiate between 15 mg of morphine and 1 ml of normal saline, so long as he (the operator) was kept in ignorance of which agent the subjects had had." It is not surprising and, indeed, to be expected, that he should find that the pain threshold was raised by both placebo and morphine. It has been repeatedly demonstrated that placebo agents, by virtue of their suggestive effect, strikingly modify pain thresholds and may simulate the effectiveness of an active analgesic. This is in keeping with the common observation that patients suffering from effects of serious tissue damage may be dramatically comforted by placebos. Furthermore, it is of interest to note that the dose-response curves for morphine, obtained by Beecher from his bedside observations, are like those published earlier in our own studies on pain threshold-raising action. According to Beecher, "it is widely stated by those who use experimental pain methods, that aspirin has no analgesic power." As a matter of fact, in our hands the pain threshold-raising effect of aspirin has always been demonstrable when the most rigid controls have been used, including studies in which neither the operator nor the subject knew whether an active agent or a placebo had been administered. Others, including ourselves, have failed to obtain, after aspirin, significant alterations of pain threshold with tests upon untrained subjects. These disagreements show the importance of care and experience in planning studies on pain and in the operation of pain threshold measuring equipment.

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I AM pleased, of course, that Dr. Hardy, Dr. Wolff, and Miss Goodell have taken the trouble to comment in detail on my article in SCIENCE, where I attempted to describe necessary controls for the study of subjective responses. I am only mildly surprised that they have focused entirely upon pain, even though this was, as stated in the article, one of 27 subjective responses we had studied.

There is good reason to dwell upon the problem of pain: both they and we have had our principal experience with this response. There is a further practical reason: I wrote the article in the hope of persuading some of those who study subjective responses, in particular analgesia, and the effectiveness of analgesic agents, to consider a little more fully than in the past, the need for and the nature of, the necessary controls. Analgesics constitute only one aspect, albeit a very important aspect, of the pain problem. We have used pain and its relief as valid material for study of the *general* problem of controls in this field. We have worked slowly and cautiously. Until the essential controls are sharply and clearly established, any work is perilous. One cannot establish universals from a limited experience, of course; but our experience with pain stood us in good stead in study of the other subjective responses mentioned. On the basis of our total experience to date, the generalizations recorded in the article appeared to be justified. I can say to Dr. Hardy, Dr. Wolff, and Miss Goodell that I had no intention of emphasizing analgesics, or even pain, in my article. I thought that was evident.

It is no more possible to study pain broadly and soundly without studying its relief than it is to study sleep without studying wakefulness (*cf.* Kleitman). Many kinds of attacks on the complex pain problems are, of course, possible and desirable. Much of our work has been concerned with measuring pain in terms of its relief. This is indirect, to be sure; biology and chemistry are shot through with equally indirect techniques—for example, the simple determination of the acidity of a solution by the quantity of standard alkali it takes to neutralize it is indirect. It seems rather extreme to call our procedure "studying pain by avoiding it." If this is what we have done, we make no apology for doing so. The technique has been fruitful.

As far as this goes, Dr. Hardy, Dr. Wolff, and Miss Goodell have time and again used their method as a means for studying analgesic agents. It is puzzling to me, and it seems paradoxical, too, that they emphasize "the sensation of pain itself" as presumably elicited with their method and yet use this for the study of analgesic agents. At the same time they stress, rightly, that the *reaction* to pain is an important component of the experience. It is plain that the reaction of the man in a sickbed, where his pain may be a warning of disaster, will not be the same as the reaction of a well and comfortable man in the laboratory subject to a momentary pricking sensation. There are, certainly, traps in the forest.

Dr. Hardy, Dr. Wolff, and Miss Goodell have always attached importance to the reaction to pain as a fundamental part of the process, just as we have done. Since this reaction depends in large part upon its meaning to the subject—a meaning certainly influenced by its origin (whether disease or trauma, on the one hand, or the laboratory, on the other)—it seems to us reasonable to separate pain on the basis of its origins and significance to the subject; that is, experimental or pathological. I am surprised that they found this rather obvious point a "confusing . . . dichotomy."

I should have supposed that we had made clear enough the reasons for our objections to the method of Hardy, Wolff, and Goodell. It did not work in our hands. Admittedly, this might or might not be relevant. We did not rest on our own experience. We enlisted the help of a responsible investigator who had worked happily with the method for years and had published a number of articles based upon it. When he repeatedly failed to distinguish between a large dose of morphine and a placebo (as long as he was in ignorance of what had been used), there did not seem to us to be any point in looking for subtleties with the method—as for example, trying to distinguish between two analgesic agents. Nor did we leave matters here; we went to a number of investigators in the fields of pharmacology and physiology, men who are well known for their painstaking skill in experimentation and sound critical judgment. They *all* reported that their experience had been exactly like ours with the Hardy-Wolff-Goodell method. I certainly have no intention of trading on their names. We discovered them with only a little inquiry. I recommend that Dr. Hardy, Dr. Wolff, and Miss Goodell ask the same questions.

With this background, and for the other reasons stated in our published papers, we became skeptical of the usefulness of experimental pain methods in man for the evaluation of analgesic agents. There is nothing contradictory in our statement that the experimental pain method *may* have some usefulness in animals for a study of pain sensation, but this is outside our own experience. Investigators like Nathan B. Eddy have found experimental pain methods useful in animals for evaluating analgesics, and we defer to their experience. But I wish someone would explain to me how these methods work, when all the experimental pain methods in animals depend upon reflex depression, and yet one can hardly understand how, in the doses used, the analgesics can depress reflexes. There is an interesting problem here. This does not deny that some help may be obtained from animals, but man remains the animal of necessity for the final evaluation of subjective responses.

Hardy, Wolff, and Goodell say that "pain sensation must be separated from associated pain reaction patterns." I heartily agree that this is desirable, but I doubt that it has been done as yet. They have confused this doubt of mine (reasons for it are stated above) with a denial of its importance. Of course it

is important, but I have seen no convincing evidence that it has been done or, for that matter, that it can be done.

In their last paragraph Hardy, Wolff, and Goodell appear to make the astonishing suggestion that the reason we failed to use their method successfully was because of the well-known effectiveness of a placebo in treating pain. We have dwelt upon this fascinating fact time and again, but if their method does not distinguish between a large dose of morphine and a placebo, where can one depend on it?

I should like to close by commenting on a matter that seems to me to be fundamental. We are firmly convinced that dependable information free from bias in this difficult field can be obtained only when *neither the subject nor the observer* knows what has been used. Now, when others have failed to confirm their work (as with aspirin, for example), Hardy, Wolff, and Goodell have for years insisted that their success where others failed was due to the fact that they used a few highly trained, experienced subjects over long periods. As everyone knows, the analgesic drugs produce a number of subjective responses which may or may not be related to pain relief—euphoria, for example, "giddiness," and so on. In other words, highly experienced subjects who know in general that they are involved in studies on analgesics are certainly not unaware when a narcotic is used and when a placebo is used. They know all too well what responses are expected. In short, I do not believe it is possible to fulfill the essential requirement of the unknown technique with such drug-wise, sophisticated subjects. This is not by any means to impute dishonesty to them. I would not trust data obtained by myself or by any other observer who knew what was used. Dr. Hardy, Dr. Wolff, and Miss Goodell evidently now also subscribe to the importance of the "double-blind" experiment (see their last paragraph). I doubt if they can achieve it with their highly trained, drug-wise subjects. The investigator I referred to above got good elevation of threshold when he knew morphine was used. He got no dependable data when he did not know what was used.

The highly trained subjects used by Hardy, Wolff, and Goodell came to have a vested interest in the outcome. To be sure, learning on the part of the subjects is always a hazard, but far more so with the group just mentioned than with a group that does not know what to expect, who have no interest in how the data come out, and who are discontinued as subjects after a few doses of the drugs.

It is absolutely essential that unconscious bias be eliminated here. Subjects who know how to recognize the subjective sensations of analgesics and who have an interest in the outcome cannot be considered as unbiased. I am obliged to continue to question the validity of any such experiments when either the subject or the observer is aware of what was used.

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Book Reviews

Science and the Social Order. Bernard Barber. Glencoe, Ill.: Free Press, 1952. 288 pp. $4.50.

It is one of the anomalies of our time that in a period of history when science is markedly influencing the social order this book is probably the first complete study of the subject. Robert K. Merton discusses in his foreword the reasons for the strange neglect of this field. The natural scientists are still, by and large, uninterested in the social sciences, and the social scientist has been afraid to speak of the natural sciences in which he has not been trained. A third factor that may have retarded this study is the fact that for some time the subject was almost monopolized by writers who accepted the Marxian analysis of history.

The book collects under one cover, and in a very readable style, the bulk of what is known on the mutual interaction of science and society. It attempts to correlate the material on the basis of techniques and concepts that have proved of value in other areas of sociological thought.

Barber's conclusions are very tentative—as they should be on the basis of so little established data. Only at the end, where he discusses the role and feasibility of the social sciences, does he become eloquent in defense of his field. His defense is convincing except on one point. He seems to underestimate the possibility of misuse of the social sciences on the basis of his statement that human beings will not let themselves be made into utter automatons. But great suffering can be caused long before this stage is reached, and it requires continual vigilance and a knowledge of what science can and cannot do, if we are not to acquiesce in programs labeled "scientifically established," when in fact scientific knowledge is applied to inhuman ends.

The book begins with a discussion of the nature of science and devotes an all too brief chapter to the sociological basis underlying the historical development of science. The major part of the book then deals with contemporary science both in liberal and authoritarian societies, and specifically with the social organization of science in America in the universities, in industry, and in government. A chapter on the respective roles of the individual and society in the progress of science makes fascinating reading, followed by the most provocative part of the book, deal-

ing with the social consequences of science, the social responsibility of science, and the question of whether science can be planned.

The criticism of Norbert Wiener's position is not well founded, for the author approves Bridgman's barring Nazi scientists from his laboratory, implying that he would also approve the refusal of scientists to work for the Nazis. But such a stand is in essence no different from Wiener's refusal to publish data in peacetime that would immediately be applied to guided-missile research. If the principle is accepted that the scientist must draw the line at some point as to the exploitation of his knowledge by society, and if, as is also done in this book, the stand is taken that respect for individual conscience is a sociological factor favoring the development of science, then Wiener's stand must be accepted as a valid exercise of social responsibility, even if the author cannot agree with the point where the line is drawn. The studies of J. U. Nef summarized in his *War and Human Progress* show that Wiener's position was widely held in the early period of modern science.

One might wish that every scientist would ponder the implications of this study. It is not by any means a subject of purely academic interest, for the interaction of science and society is molding our future, and much can be done to guide the interaction wisely.

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Thermodynamics and Statistical Mechanics. William P. Allis and Melvin A. Herlin. New York–London: McGraw-Hill, 1952. 239 pp. $6.00.

This book has been designed as a text for a half-year course for college seniors majoring in physics. Within the confines of such a course, the authors have endeavored to present both the fundamental ideas of thermodynamics, and enough statistical mechanics to give the student some idea of the statistical basis of thermodynamic laws. This has made it necessary to limit the presentation of both fields rather stringently.

The treatment of heat and thermodynamics has been simplified by rigid restriction of the illustrative materials—only pure substances are considered, and the only force discussed is hydrostatic pressure. Later, in the section on statistical mechanics, magnetization is considered, and the student sees the formalism in terms of variables other than P, V, T.

Statistical mechanics is treated from the Boltzmann-Planck point of view. The microstates of systems are described in terms of cells in phase space; the existence of a natural cell size, h^3 in three-dimensional phase space, is deduced from the third law of thermodynamics and the Sackur tetrode equation. In this part of the book the illustrative material is abundant and varied. It includes discussion of gases, magnetism, specific heat theory, Brownian movement, thermal noise and radiation, He II, and electrons in metals. Here, space limitations are met by extreme simplifications of the discussion, occasionally to the point of misleading superficiality. College seniors are likely to find the range of illustrative material intriguing, but the reviewer is inclined to wish that the authors had followed the pattern established in their treatment of thermodynamics, with fewer illustrations more completely developed.

On the whole, this is an attractive text, with many illustrative problems and a good index.

H. M. JAMES

Department of Physics, Purdue University

Scientific Book Register

Phosphorus Metabolism: A Symposium on the Role of Phosphorus in the Metabolism of Plants and Animals, Vol. II. Sponsored by the McCollum-Pratt Institute of The Johns Hopkins University. William D. McElroy and Bentley Glass, Eds. Baltimore: Johns Hopkins Press, 1952. 930 pp. Illus. $11.00.

Water: Miracle of Nature. Thomson King. New York: Macmillan, 1953. 238 pp. $3.50.

Races of Maize in Mexico: Their Origin, Characteristics and Distribution. English ed. of *Razas de Maíz en Mexico.* E. J. Wellhausen, L. M. Roberts and E. Hernandez X., with collab. of Paul C. Mangelsdorf. Cambridge, Mass.: Bussey Inst., Harvard University, 1952. 223 pp. Illus.

Léon Fredericq: Un Pionnier de la Physiologie. Volume publié à l'occasion du Centenaire de sa naissance. Z. M. Bacq and M. Florkin, Eds. Liège: Sciences et Lettres, 1953. 232 pp. Illus. 210 Belg. fr.

Kinetics and Mechanism: A Study of Homogeneous Chemical Reactions. Arthur A. Frost and Ralph G. Pearson. New York: Wiley; London: Chapman & Hall, 1953. 343 pp. Illus. $6.00.

Lillie's Development of the Chick: An Introduction to Embryology. 3rd ed. Revised by Howard L. Hamilton. New York: Holt, 1952. 624 pp. + plates. $8.50.

Possums. Carl G. Hartman. Austin: Univ. Texas Press, 1952. 174 pp. Illus. $6.00.

Principles of Organic Evolution. Arthur Ward Lindsey. St. Louis: Mosby, 1952. 375 pp. $5.75.

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Thermionic Vacuum Tubes and Their Applications. 6th ed. W. H. Aldous and Edward Appleton. London: Methuen; New York: Wiley, 1952. 160 pp. Illus. $2.00.

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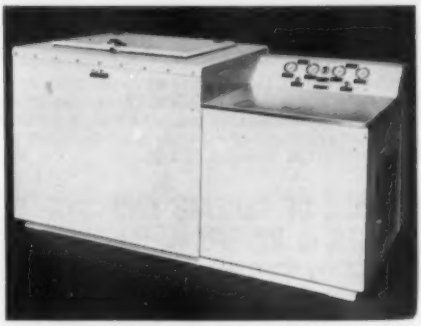

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Fishing Industry Research Institute. Fifth Annual Report of the Director. Apr. 1, 1951–Mar. 31, 1952. Cape Town, South Africa: Fishing Industry Research Inst., 1952. 19 pp.

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Time and Universe for the Scientific Conscience. Martin Johnson. New York: Cambridge Univ. Press, 1952. 42 pp. 50¢.

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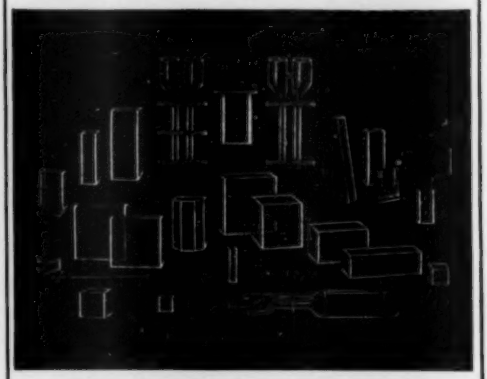

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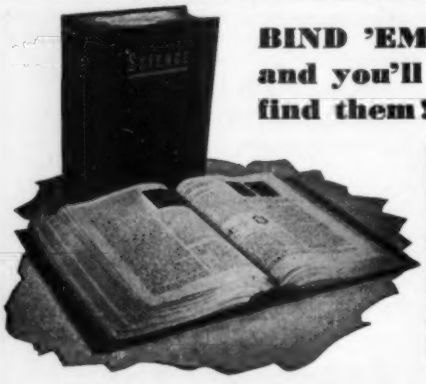

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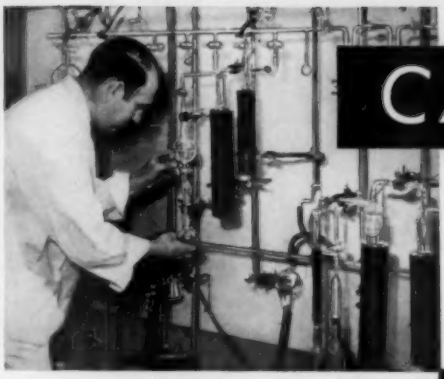

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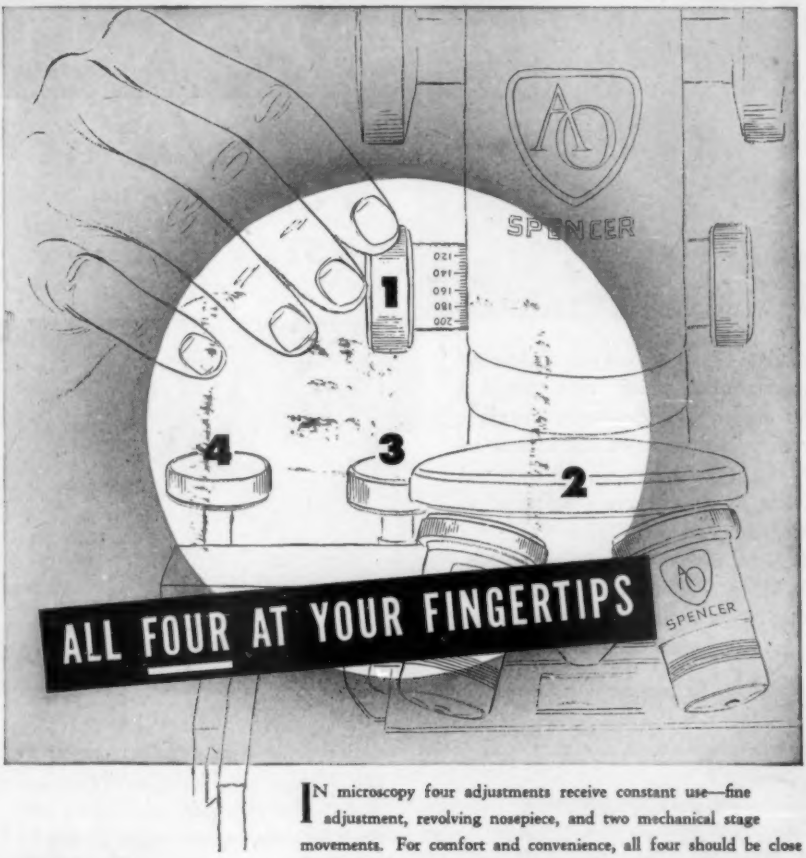

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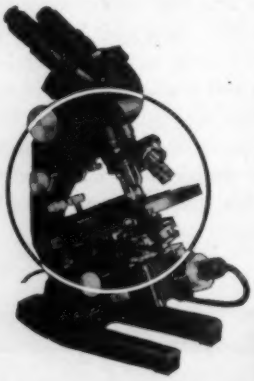

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